CASE REPORT

REVISED Case Report: Odontogenic carcinosarcoma arising from premature odontoma with immunohistochemical profile [version 2; peer review: 1 approved with reservations, 2 not approved]

Previously titled: Case Report: Odontogenic carcinosarcoma arising from ameloblastic fibrodentinitoma with immunohistochemical profile

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V2 First published: 12 Jun 2020, 9:603
<https://doi.org/10.12688/f1000research.23969.1>

Latest published: 15 Dec 2020, 9:603
<https://doi.org/10.12688/f1000research.23969.2>

Abstract

Odontogenic carcinosarcoma is an extremely rare mixed malignant odontogenic neoplasm in which both the epithelial and the ectomesenchymal components are cytologically malignant. Owing to the scarcity of the reported cases, the clinical behavior of odontogenic carcinosarcoma remains unexplored. The present work reports a case of odontogenic carcinosarcoma of the mandible with the detailed immuno-histochemical profile. A 28-year-old male presented with a left painless swelling, which recurred after hemimandiblectomy of the lesion. Complete excision of the lesion with a wide safety margin was performed. The histopathological examination revealed cytological malignant features in the follicles as well as in the ectomesenchyme. The immuno-histochemistry demonstrated evidence of epithelial mesenchymal transition. After nine months, the patient demonstrated recurrence in the infra-temporal fossa. Odontogenic carcinosarcoma is a rare highly aggressive malignant odontogenic tumor. Positive expression of smooth muscle actin and vimentin in the epithelial component is a useful aid in the diagnosis of odontogenic carcinosarcoma.

Keywords

Odontogenic carcinosarcoma, α-smooth muscle actin, vimentin, epithelial mesenchymal transition, Ki-67.

Open Peer Review

Approval Status **✗ ? ✗**

	1	2	3
version 2 (revision) 15 Dec 2020		? view	✗ view
version 1 12 Jun 2020	✗ view	✗ view	

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the **Oncology** gateway.

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Author roles: Salem HMWM: Conceptualization, Funding Acquisition, Resources, Supervision, Writing – Review & Editing; **Ahmed Mohamed Mahmoud Badawy S:** Conceptualization, Formal Analysis, Methodology, Project Administration, Software, Visualization, Writing – Original Draft Preparation; **Amer HW:** Data Curation, Investigation, Methodology, Supervision, Validation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the fast track Research Funding Program.

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How to cite this article: Salem HMWM, Ahmed Mohamed Mahmoud Badawy S and Amer HW. **Case Report: Odontogenic carcinosarcoma arising from premature odontoma with immunohistochemical profile [version 2; peer review: 1 approved with reservations, 2 not approved]** F1000Research 2020, 9:603 <https://doi.org/10.12688/f1000research.23969.2>

First published: 12 Jun 2020, 9:603 <https://doi.org/10.12688/f1000research.23969.1>

REVISED Amendments from Version 1

We changed the title because it didn't follow the nomenclature stated in the new WHO classification.

We tried to improve the histopathological description of the lesion.

We edited the histopathological [Figure 3](#) & [Figure 4](#) to clarify the features of the lesion.

We repeated the ki67 staining and measured the area percent by leica Qwin software [Figure 6](#).

We contacted the surgeon to improve the follow-up information of the patient.

We tried to improve the discussion as recommended by the reviewer.

We wrote the take-home message in the conclusion section.

Any further responses from the reviewers can be found at the end of the article

Introduction

Malignant odontogenic tumors are rare group of malignant neoplasms that arise from odontogenic remnants¹. One of these neoplasms is odontogenic carcinosarcoma (OCS), an extremely rare mixed malignant odontogenic neoplasm in which both the epithelial and the ectomesenchymal components are cytologically malignant². In the 1992 World Health Organization (WHO) classification of tumors, OCS was included in the malignant odontogenic tumors after Tanaka and co-workers (1991) first reported an odontogenic tumor with a mixture of malignant epithelial and ectomesenchymal components³. In the 2005 WHO classification, the tumor was removed due to an absence of current diagnostic criteria⁴. OCS has been added again in the 2017 edition because of the availability of cases with adequate diagnostic immunohistochemical and molecular criteria^{5,6}. Owing to the scarcity of reported cases - only eleven reported cases in the English literature - OCS clinical behavior remains unexplored^{7,8}. In the current work, we report a case of OCS with the detailed clinical, radiographic, histopathological and immunohistochemical description.

Case report

In December 2016, a 28-year-old Egyptian male patient working as an accountant was referred to the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Cairo University, with a complaint of painless swelling of six months duration in the left side of his face measuring 7 × 6 cm. The patient had a pathological report of an incisional biopsy, performed outside our institute, which was diagnosed as ameloblastoma. There were no palpable lymph nodes. Intra-oral examination revealed an absence of the lower left molars with a fistula opening on the alveolar crest with no oozing pus.

A cone beam computed tomography examination revealed an ill-defined multilocular osteolytic lesion with fine radiopacities extending from the lower left second premolar up to the ramus.

There was prominent cortical expansion with areas of perforation ([Figure 1](#)). A hemi-mandibulectomy was performed based on the incisional biopsy diagnosis and the pathological fracture of the mandible. The ramus was totally destroyed and the tumor was invading the masseter muscle ([Figure 2](#)). Differential diagnosis was made based on the clinical examination, radiographic appearance and gross examination as: ghost cell odontogenic carcinoma, ameloblastic carcinoma, ameloblastic fibrosarcoma, ameloblastic carcinosarcoma, calcifying epithelial odontogenic tumor, atypical type of ameloblastic fibro-dentinoma⁹ and ameloblastoma.

Histopathological examination revealed hypercellular follicles and strands of odontogenic epithelium, that were lined peripherally by multilayers of tall columnar ameloblast like cells. The center of the follicles was filled by stellate reticulum like cells, which were basaloid in appearance in some follicles. In between the follicles, there was a highly cellular primitive ectomesenchyme resembling dental papilla. Some of the nuclei of the ectomesenchymal cells were hyperchromatic. In some fields, dentinoid matrix was detected around the epithelial strands ([Figure 3A](#)). Based on the histopathological examination and the case report of Giraddi and Garg 2012⁹, and because it was before the publication of the new WHO classification of 2017, a diagnosis was made of ameloblastic fibro-dentinoma (atypical type).

Figure 1. Cone beam computed tomography of odontogenic carcinosarcoma, axial view showing the multilocular lesion extending from the left lower second premolar to the condyle involving the whole ramus with buccal perforation. There was scattered radiopacities closely related to the impacted first molar. The second molar was displaced against the angle of the mandible.

Figure 2. Gross examination: (A) Hemi-mandibulectomy with safety margin including the masseter muscle. (B) Cross-section of the resected specimen showing the fleshy neoplasm and the impacted first molar. (C) Top view of the resected specimen showing the necrotic fistula on the alveolar ridge. (D) The excisional specimen of the recurrent lesion.

Figure 3. Histopathological examination of the resected specimen (hematoxylin and eosin stain, X100). (A) Microscopic image showing odontogenic epithelial follicles formed of ameloblast-like cells on the periphery and stellate-reticulum like cells on the center, which were surrounded by primitive ectomesenchyme resembling dental papilla. Dentinoid material was detected in contact with the epithelial follicles (black arrows). (B) Microscopic image showing another field which was hypercellular in both components with mild pleomorphism and hyperchromatism.

After nine months and after the publication of 2017 WHO classification, the patient returned with another large painless swelling in the left temporal and infra-temporal fossa of three months duration. There were no palpable lymph nodes. An oral and maxillofacial surgeon used local anesthesia and an intra-oral approach to completely excise the recurrent lesion (Figure 2D). Augmentin 1gm tablet/12 hours for five days and

anti-inflammatory medication were prescribed for the patient after the surgery. Histopathological examination revealed highly cellular neoplasm, which showed cellular atypia and increased nuclear cytoplasmic ratio in both epithelial and ectomesenchymal components. The typical ameloblastic architecture of the epithelial follicles was lost in some areas. The ectomesenchymal component showed large pleomorphic cells (Figure 4).

Figure 4. Histopathological examination of the recurrent lesion (hematoxylin and eosin stain): **(A & B)** Microscopic image showing hypercellular epithelial follicles with plump hyperchromatic and pleomorphic cells and absence of the stellate reticulum cells in the center, along with hypercellular ectomesenchyme, the basement membrane was vague in some areas (black arrows) (X200). **(C)** Microscopic image showing epithelial follicle with pleomorphism, hyperchromatism, and increased nuclear-cytoplasmic ratio. The basement membrane was lost in some areas (black arrows) (X400). **(D)** Microscopic image showing atypia in ectomesenchymal component with increased mitosis, bizarre shaped nuclei and increased nuclear/ cytoplasmic ratio (X400).

The epithelial nests showed strong membranous positivity with AE1/AE3, while vimentin stained the ectomesenchyme diffusely and the epithelial nests patchily. Alpha-smooth muscle actin (α -SMA) showed positivity in the endothelial cells as well as in scattered epithelial cells (Figure 5). Ki-67 index was measured by Leica Qwin software and was 7.46% in the epithelial component, while in the ectomesenchymal component it was 2.78% (Figure 6). Based on the histopathological and immunohistochemical findings, the case was diagnosed as OCS. In 2019 and after nearly a year and a half, the patient came to Oral & Maxillofacial Surgery department for the reconstruction surgery and the examination revealed neither a recurrence nor complications.

Discussion

OCS is a rare biphasic malignant odontogenic neoplasm that has the same architecture of ameloblastic fibroma, in which the epithelial and the ectomesenchymal components are cytologically malignant. It can develop *de novo* from odontogenic remnants

or as a transformation from a preexisting odontogenic benign or malignant neoplasm⁶. This transformation may be attributed to multiple surgical procedures or recurrences of the neoplasm². The present case arose from a preexisting immature odontoma which was formerly called ameloblastic fibrodentinoma. Kunkel *et al.* (2004), DeLair *et al.* (2007) and Chikosi *et al.* (2011) reported cases aroused from ameloblastic fibrosarcoma, ameloblastic fibroma and ameloblastoma, respectively^{2,10,11}.

Our case was a 28-year-old male with the lesion affecting the posterior mandible. In the English literature, there was a male predilection and only one case that occurred in maxilla⁴. The most common radiographic picture of OCS is ill-defined multilocular radiolucency with cortical perforation⁶. The current case showed multiple radiopacities; may be due to the preexisting immature odontoma.

OCS must be distinguished from ameloblastic fibrosarcoma, in which the ectomesenchymal component only shows cellular

Figure 5. Immunohistochemical staining (X200): **(A)** Microscopic image showing strong membranous expression of AE1/AE3 in the epithelial component with the ectomesenchymal component being completely negative. **(B)** Microscopic image showing strong diffuse cytoplasmic expression of vimentin in ectomesenchymal component along with patchy expression in the epithelial component. **(C)** Microscopic image showing cytoplasmic expression of α -SMA in the endothelial cells and scattered epithelial cells.

Figure 6. Immunohistochemical staining and analysis of Ki-67 (X200): **(A)** Microscopic image showing strong positive reaction of both epithelial and ectomesenchymal cells. **(B)** Screenshot showing the measurement of the area percent of Ki-67 expression of epithelial component using Leica Qwin software. **(C)** Screenshot showing the measurement of the area percent of Ki-67 expression of mesenchymal component.

atypia, and spindle cell variant of ameloblastic carcinoma, which lacks the ectomesenchymal component²⁻⁸. In the present case, there was a patchy positive expression of vimentin in the epithelial component. This could be explained as OCS undergoes epithelial mesenchymal transition, a process in which the polarized immotile epithelial cell changes to gain the mesenchymal phenotype and indicates more aggressive behavior of the neoplasm^{7,12,13}.

In accordance with Dos Santos *et al.* (2018), α -SMA staining in the current case showed scattered staining in the epithelial cells⁴. Its expression in the epithelial cells could be attributed to the epithelial mesenchymal transition process; which increases the potentiality of the tumor cells to invade and metastasize¹⁴.

The proliferative index Ki-67 in our case was around 7.5% in the epithelial component and 3% in the ectomesenchymal component. This is in accordance with the work of Dos Santos *et al.* (2018) and Soares *et al.* (2019), who found that Ki-67 index was higher in the epithelial component than the ectomesenchymal component⁴⁻⁷.

Regarding the clinical behavior of OCS, it is a highly aggressive highly recurrent malignant neoplasm⁷. In our case, the patient encountered recurrence of the lesion after 9 months follow up with no evident metastasis. In the English literature, six out of the eleven cases showed recurrence of the lesion and only 4 cases showed metastasis; whether to lungs or lymph nodes⁶. Kunkel *et al.* (2004) reported the late metastasis of their case; which was evident about 5 years after the first diagnosis¹⁰. There were five out of the eleven cases encountered death⁶,

one of them was actually due to systemic complication after the resection of the lesion⁷.

The principle line of treatment, as with other malignant odontogenic neoplasms, is surgical resection with a wide safety margin along with neck dissection. However, adjunctive radiotherapy is still a matter of question, and it may be helpful in cases with soft tissue invasion⁶.

Conclusion

OCS is an extremely rare odontogenic malignant neoplasm that shows very aggressive clinical behavior with multiple recurrences and possible metastasis. Close long follow-up is recommended; due to the possible late metastasis of the lesion. Immunohistochemical staining with vimentin, α -SMA and Ki-67 is helpful in the diagnosis of OCS.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Consent

Written informed consent for publication of their clinical details or clinical images was obtained from the patient.

Acknowledgments

This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the fast track Research Funding Program. Moreover, we are sincerely grateful for our colleges in Oral & Maxillofacial Surgery department, Faculty of Dentistry, Cairo University.

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Current Peer Review Status:

Version 2

Reviewer Report 23 February 2021

<https://doi.org/10.5256/f1000research.31317.r79791>

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John Wright

Department of Diagnostic Sciences, Texas A&M College of Dentistry, Dallas, TX, USA

I have reviewed the case report of an odontogenic carcinosarcoma arising from a premature odontoma and I do not agree with the diagnostic interpretation rendered. While the description provided is more supportive of the diagnosis, the illustrations provided do not in my opinion confirm the diagnosis. The illustrations are not of the highest quality. In Fig 3, there is nothing to suggest malignancy and I would question the presence of dentinoid. I would have diagnosed this as ameloblastic fibroma. Fig 4 is not obviously malignant to me either, either component. There is some nuclear hyperchromasia in the epithelial component but this does not appear malignant. I admit there is increased cellularity in the ectomesenchymal component along with some limited cytologic atypia, which is concerning but this component is not obviously malignant to me either. The Ki-67 reactivity is more consistent with a benign diagnosis. I don't think the IHC in Fig 5 adds any evidence for a malignant diagnosis. The cytokeratin and vimentin reactivity would be expected with a benign or malignant diagnosis and the SMA illustrated shows only the vessel walls. At best from the illustrations provided, this might be called an atypical ameloblastic fibroma but I am not convinced either component is malignant and must recommend against its indexing.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I have 40 years of surgical pathology experience with one of the worlds largest biopsy services. I am a past President of the American Board of Oral and Maxillofacial Pathology. I was a member of the WHO working group that published the most current WHO classification of odontogenic cysts and tumors. I am currently a co-editor writing the new AFIP fascicle on head and neck pathology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 13 January 2021

<https://doi.org/10.5256/f1000research.31317.r76168>

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João Paulo Silva Servato

University of Uberaba, Uberaba, Brazil

Most of the required topics were improved in this new version. Although that, some minors points still need some corrections:

1. The title of the manuscript, the diagnosis of the first Histopathological examination and the Figure 3 legend, should be totally reconsidered by the authors to attend the new WHO classification and current nomenclature.
2. Ki-67 image (Figure 06) must be improved to clearly demonstrate the high levels of Ki-67 tagging in both epithelial and mesenchymal components, specially in high pleomorphic areas.
3. The percentual measurement of Ki-67 expression areas, using Leica Qwin software, appears to not validate the picture seen in Figure 06 (A). Analysis/figure should be revised.

Is the background of the case's history and progression described in sufficient detail?

No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to

future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Oral and maxillofacial pathology; Oral medicine; Immunology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 30 September 2020

<https://doi.org/10.5256/f1000research.26443.r69312>

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João Paulo Silva Servato

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1) Is the background of the case's history and progression described in sufficient detail?

Partly - In reason to understand OCS progression and outcomes, more follow up details should be addressed.

Moreover, the authors should attend to the new WHO classification nomenclature. As stated by Speight PM, and Takata T., 2018: "the ameloblastic fibrodentinoma and ameloblastic fibro-odontoma have been removed as distinct entities"¹. In this way, the nomenclature should be reviewed.

2) Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No - Please, improve the details in histopathological and immunohistochemical profile.

2.1) High power field images is needed to improve the recognition of the main expected features, as described by El-Mofty, S. K., in the 2017 WHO blue book "The cells in the sarcomatous

component are markedly pleomorphic, with enlarged and bizarre nuclei and occasional multinucleation and mitosis. The epithelial component is frankly malignant, with large hyperchromatic nuclei and an increased N:C ratio. The typical ameloblastic features such as peripheral nuclear palisading and inner stellate reticulum may be lost focally."²

In the same way, Ki-67 images must be improved to clearly demonstrate the high levels of Ki-67 tagging in both epithelial and mesenchymal components.

3) Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly, the discussion section should be expanded to access the relevance of this case in the understand of OCS main epidemiological characteristics, histopathological features, the biological profile and its prognosis/ behavior.

Moreover, as describe in CARE guidelines, this section must describe:

- a) Strengths and limitations in your approach to this case.
- b) The rationale for your conclusions.
- c) The primary "take-away" lessons from this case report.

4) Is the case presented with sufficient detail to be useful for other practitioners?

No, since it do not attended to most recent WHO classification and to CARE guidelines.

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Oral and maxillofacial pathology; Oral medicine; Immunology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 15 Dec 2020

Sarah Ahmed Mohamed Mahmoud Badawy

First, we can't thank you enough for your sincere and detailed review. We made a second version of the article with the revisions you recommended in your review; as follow:

- We did contact the surgeon to collect more details about the follow-up of the patient.
- We changed the nomenclature of "ameloblastic fibroblastoma" as you recommended, and clarified the reason why we diagnosed it like that.
- We changed and added histopathological figures as you recommended with more detailed interpretation.
- We repeated the ki67 staining and analysed it with the image analyser Leica QWin software.
- We tried to improve the discussion part as you recommended to follow CARE guidelines.

We hope that our revisions meet your expectations. Again, thank you for your precious time.

Competing Interests: No competing interests

Reviewer Report 18 August 2020

<https://doi.org/10.5256/f1000research.26443.r65932>

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I read this article and below are my comments for the journal:

- Based on documentations included in the article some points should be reconsidered by the authors.
- Diagnosis of ameloblastic fibrodentinoma does not seem to be correct, dentinoid material is not evident.
- Possibly from the beginning the lesion is an ameloblastic fibrosarcoma, therefore the microscopical aspects should be carefully reviewed including a Ki-67 staining.
- Diagnosis of carcinosarcoma should be reconsidered and most immune reactions repeated and reanalysed, including Ki-67. Interpretation of some reactions does not seem to be appropriate.

Is the background of the case's history and progression described in sufficient detail?

No

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Oral Pathology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 08 Sep 2020

Sarah Ahmed Mohamed Mahmoud Badawy

First of all, thank you for your review. I hope that in my response, I will be able to clarify some points:

- The diagnosis of the first biopsy was based on the presence of dentinoid material which is evident in figure 3.A.
- Moreover, both the ectomesenchymal and the epithelial compartments in the first biopsy showed little cellular activity without cellular atypia in all fields, there was no way to consider it as a malignancy back then without histopathological evidence; even if the clinical behavior was doubted.

- The immunohistochemical reaction of Ki67 was interpreted with 3 pathologists
- last, I wished you can mention clearly what the details do you need us to clarify in the sections of case history, physical examination, investigations, and discussion?

Thank you for your time.

Competing Interests: No competing interests were disclosed.

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