

Case Report

Ameloblastic Carcinoma: A Case Report with Immunohistochemical Profile of Claudins

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The WHO defined an Ameloblastic Carcinoma (AC) secondary type (dedifferentiated) intraosseous as a malignant neoplasm that “arises in a preexisting benign ameloblastoma. Dedifferentiated ameloblastoma is applied when morphologic features of typical ameloblastoma were noted. Microscopically, clusters or nests and islands of epithelium within a collagenous stroma are composed of a peripheral layer of polarized cells enclosing stellate to basaloid cells in the early transition of the de-differentiation stage. These cellular structures may show pleomorphism, frequent mitotic figures, indistinct cell membranes, focal necrosis, loss of cellular cohesion and infiltration along nerve bundles” [1].

According to the WHO, Unicystic Ameloblastoma (UA) represents an ameloblastoma variant, presenting as a cyst [1]. Cases associated with an unerupted tooth show a mean age of 16 years as opposed to 35 years in the absence of an unerupted tooth [2]. The mean age is significantly lower than that for solid ameloblastoma and there is no gender predilection [3], 5 to 15% of all ameloblastomas are of the unicystic type [4], but a Latin-American study showed that the unicystic type reached 60% [5]. Malignant transformation of UA is a very unusual phenomenon, and to date, only two cases of AC associated to an UA are published [6,7].

Zonula adherens and Tight Junctions (TJs) are membranar

structures for cell-cell adhesion in epithelial and endothelial cells. These structures have barrier and/or fence functions and are composed by sets of proteins regulating the transfer of ions, water, and some macromolecules (barrier function). Proteins involved in fence function maintain cell polarity, recruit signaling proteins, and control the lateral diffusion of proteins within the lipid bilayer. Additional functions of TJ proteins are regulation of cell differentiation and proliferation. TJ proteins are composed of three major integral membrane proteins: claudins, occludin, and Junctional Adhesion Molecules (JAM proteins) [8-10].

Claudins are an important group composed of 27 proteins regarded as the backbone of the TJ, they maintain cell polarity, regulating the paracellular membrane selectivity and permeability [9]. Altered expression of claudins has been related to tumorigenesis, loss of polarity, cell motility, down regulation of cell-cell adhesion, and reorganization of the cytoskeleton. These processes are associated with lack of differentiation, neoplastic progression, cell invasion, survival, aggressiveness, recurrence, and regional and distant metastases [10,11]. To date, only two studies on claudin immunoprofile in odontogenic cysts and tumors are reported [12,13]. This report describes an unusual case of an UA associated with an AC and presents the results on the immune expression of claudins 1,3 and 9, and to assess its PCNA index.

Report of Case

An 18-year-old female patient was reviewed at the Oral Surgery Clinic of the División de Estudios de Posgrado e Investigación, Facultad de Odontología, Universidad Nacional Autónoma de México in Mexico City. Her complaint was the presence of an asymptomatic, one-year duration; hard, ill-defined swelling in the bicuspid-molar area with no clinical changes to the extra-oral inspection (Figure 1a). Radiographic examination discovered a mandibular, radiolucid, unilocular image of non-corticated margins, measuring 4.3 cms approximately, located in the mandibular left premolar area (Figure 1b) with a round shaped perforation of the lingual cortex.

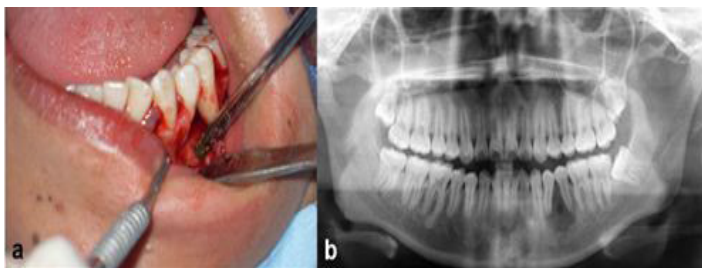


Figure 1a-b: Clinical Features of the Presented Case. Figure 1a: Clinical Aspect of the Tumor at first appointment. Figure 1b: 1st Panoramic Radiograph showing a Radio lucid ill-defined Lesion at Mandibular Right Premolar Zone. A Round Perforation is seen in the Lingual Osseous Cortex.

A clinical diagnosis of ameloblastoma was suggested and after surgical enucleation a histopathological diagnosis of unicystic ameloblastoma, mural type was rendered. The patient was lost for follow-up during 13 months, then appearing with a bigger lesion (Figure 1c). A second panoramic radiograph showed a radiolucid, multilocular lesion extending from the mandibular left canine to the second molar, showing resorption of the underlying basal border. Also, root resorption of the mandibular left canine, first and second premolars and first molar was observed (Figure 1d).

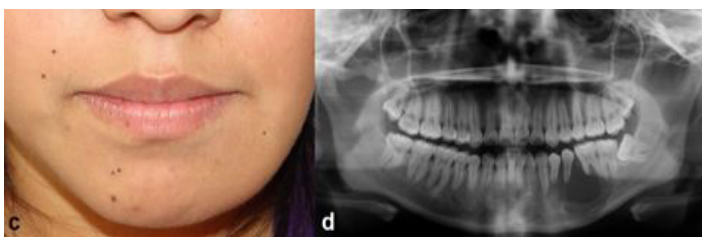


Figure 1c-d: Figure 1c: A Larger Tumoral Mass is Observed in the Right Mandible. Figure 1d: An ill-defined Multilocular Lesion with Radicular Resorption in Mandibular Right, both Premolars and 1st Molar.

For surgical excision of the tumor, the patient was sent to the Hospital General de México in Mexico City and she was admitted at the Stomatology Service. After admission, the patient was lost for additional four months and, upon presentation, she attended to the Oral and Maxillofacial Surgery Clinic with a larger tumor. Here, a second biopsy was done and a diagnosis of AC was ren-

dered. Despite our diagnosis of malignancy, she alleged her pregnancy and refused treatment. After an uncomplicated childbirth, she reappeared showing a facial, larger, hard, rapidly growing, asymptomatic swelling, measuring 12.2 cm approximately (Figure 1e). Radiographic study showed a multilocular, ill-defined, radiolucid lesion, from distal of the mandibular left central incisor to the third molar zone (Figure 1f). The patient was taken to the operating room and under general anesthesia, wide excision of the tumor, comprising from the right central incisor to the left mandibular ramus was done. H&E stained slides from several parts of the tumor were prepared, analyzed, and the previous diagnosis of AC was confirmed. Five-years after first excision of the tumor, no metastasis developed and the patient is well and alive. Clinical and surgical procedures were according for the ethical standards by the Hospital General de México, "Eduardo Liceaga".

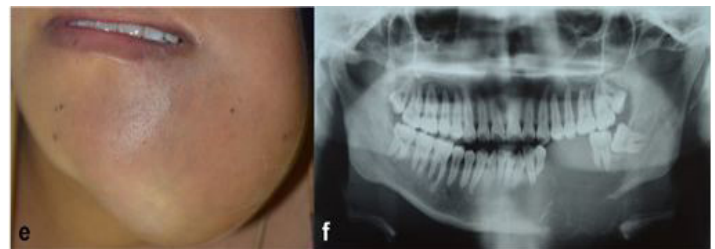


Figure 1e-f: Figure 1e: Preoperative Panoramic Radiograph showing a huge Tumor in the Affected Area. Figure 1f: Multilocular, ill-defined Radio Lucid Tumor from Mandibular Right Central Incisor to 3rd molar mesial zone. Destruction of the Basal Border, and Buccal and Lingual Cortices is observed.

Histopathology

Microscopic examination from the first specimen showed the presence of a cystic cavity lined by squamous stratified epithelium. This epithelium was several cells thick, containing reticulum cell-like areas. Also, basal cells with hyperchromatic nuclei, and basal cell palisading were identified (Figure 2a). An intracapsular mural nodule with reticular ameloblastomatous appearance, showing a basal layer of columnar cells with palisading arrangement, well-defined borders, cytoplasmic vacuolization, hyperchromatic nuclei, and nuclear polarization away from the basement membrane was seen (Figure 2b). A diagnosis of UA mural type was rendered. But unfortunately, no tissue was available for further analysis.

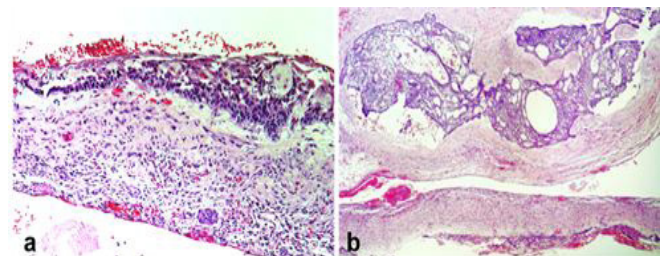


Figure 2a-b: Microscopic Features of the first Specimen Analyzed. Fig-

ure 2a: The Lining of the Specimen was Stratified Squamous Epithelium showing Ameloblastomatous Features. Figure 2b: A Mural Nodule Consisting of a Solid Ameloblastoma is Observed.

In both, the second incisional biopsy and the resected specimen, the H&E stained slides showed the presence of a malignant ill-differentiated neoplasm formed by numerous desmosome-free, densely packed epithelial cells, arranged in a solid growth pattern. Most of the specimen was composed of round, oval or polygonal malignant epithelial cells with hyperchromatic, pleomorphic nuclei, prominent nucleoli, and increased nucleus-cytoplasm ratio (Figure 3a). Additionally, several areas containing fusiform slender cells were noted (Figure 3b). We observed areas with peripherally located columnar cells and hyperchromatic nuclei, located away from the basement membrane, vesicular cytoplasm, and arranged in a palisaded fashion (Figure 3c). Sometimes, these peripheral cells were of cubic shape. In the densely packed cellular areas, we observed regions presenting a complex architecture, consisting in dissolution of the epithelial intercellular tissue with detachment of the basal and parabasal cell layers giving rise to small areas of stellate reticulum-like appearance. Neoplastic cells invading the underlying connective tissue were observed too. Additionally, the subjacent connective tissue showed cellular disruption, increase of the local vascular bed, vascular dilatation, edema, and presence of multinucleated giant cells (Figure 3d).

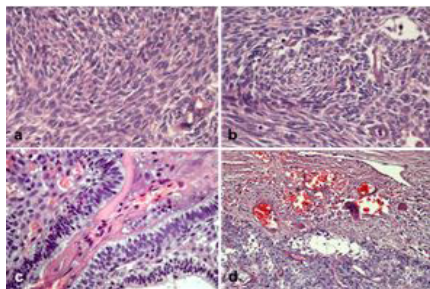


Figure 3a-d: Microscopic Features of the Second Incisional Biopsy. Figure 3a: Malignant Epithelial Cells with Hyperchromatic and Pleomorphic Nuclei, Prominent Nucleoli, increased Nucleus-Cytoplasm Ratio, and variable Morphology were seen composing the main part of the Tumor. Figure 3b: Groups of Fusiform Malignant Cells are shown. Figure 3c: Peripheral Cells of the Tumor were columnar or cubic with Ameloblastomatous appearance. Figure 3d: Complex area showing Rupturing of the Basement Membrane, Neoplastic Cells Invading the Connective Tissue, Numerous Blood Capillaries and Multinucleated Giant Cells are observed.

In the additional material, atypical cells of indistinct cell boundaries with loss of cellular cohesion and absence of stellate reticulum-like structures are shown (Figure 4a). Abnormal mitoses were rarely seen and only one small area with squamous differentiation was found (Figure 4b). These closely packed neoplastic cells were associated with abundant capillary blood vessels immersed in thick rims of desmoplastic fibrous connective tissue (Figure 4c). Characteristically, a thick capsule of fibrous connective tissue was

seen separating the neoplasm and the surrounding bone (Figure 4d). Also, small groups of ill-differentiated malignant neoplastic cells infiltrating the adjoining bone were noticed (Figure 4e). In some small nerves, early malignant invasion was observed (Figure 4f).

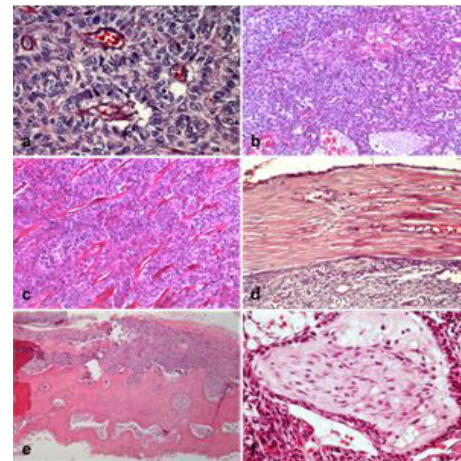


Figure 4a-f: Microscopic Features of the Second Incisional Biopsy, Figure 4a: Numerous Atypical Cells of Indistinct Cell Boundaries and Loss of Cellular Cohesion with no Stellate Reticulum-Like Structures are shown. Figure 4b: Scanty Abnormal Mitoses and one Area with Squamous-Like Differentiation is observed. Figure 4c: Intratumoral Capillary Blood Vessels with a thick rim of Desmoplastic Tissue was frequently seen. Figure 4d: The Tumor was surrounded by a Thick Capsule of Collagenous Tissue. Figure 4e: Bone Surrounding the Analyzed Neoplasm Contained Numerous Atypical Malignant Cells. Figure 4f: Small Nerve Invaded by Malignant Cells.

Immunohistochemical Profile

(Table 1) shows the immunohistochemical characteristics of antibodies applied. Only immunopositivity to claudin-1 was obtained with no immunostaining with claudins -3 and -9. In the epithelial ameloblast-like and cubic peripheral cells, cytoplasmic immunostain was detected in the apical side (Figure 5a). In the central closely packed malignant neoplastic cells claudin-1 immunoexpression was slight and cytoplasmic (Figure 5b). Approximately 15% of the neoplastic cells showed nuclear positivity and interestingly, we found zones showing two different kinds of neoplastic cells. The first type showed moderate cytoplasmic immunopositivity and were located close to slightly stained malignant cells (Figure 5c). We noted many cells with very intense nuclear immunopositivity (Figure 5d). These cells were in peripheral position mainly, sometimes they were located adjacent to the epithelial peripheral layer and rarely, they were found in a more central location.

Antibody		Dilution	Control tissue
Claudin-1	Rabbit, anti-human, IgG1, GeneTex, USA.	1:100	Human skin

Clau- din-3	Rabbit, anti-human, IgG1, GeneTex, USA.	1:100	Human small intestine
Clau- din-9	Mouse, anti-human, IgG1, GeneTex, USA.	1:100	Human colon carcinoma
PCNA	Mouse, anti-human, IgG2a, Santa Cruz, USA.	1:100	Human colon carcinoma

Table 1: Characteristics of Antibodies Applied for Immunohistochemistry.

It was noted that in the complex areas, the neoplastic basal cells and those in the connective tissue showed moderate cytoplasmic and nuclear immunostaining, associated with intensely positive multinucleated giant cells (Figure 5e). Endothelial cells of the intratumoral blood vessels were negative or showed discontinuous immune expression to claudin-1 (Figures 5a-5d) contrasting with those from the extratumoral vessels showing strong immunopositivity (Figure 1f). Claudin immunoreaction was similar in polygonal, round, oval and fusiform cells (Figure 5f).

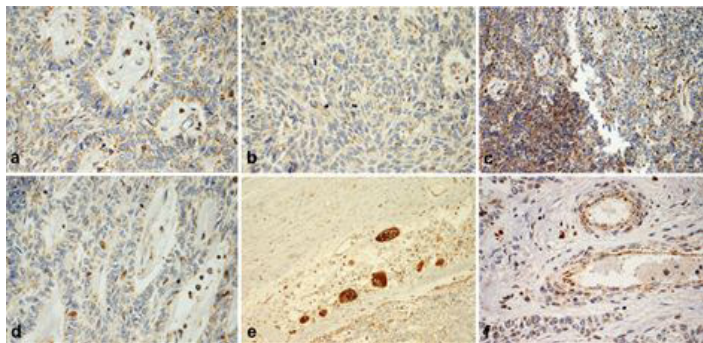


Figure 5a-f: Tumor Cell Immunoexpression to Claudin-1. Figure 5a: Cytoplasmic Positivity is seen in the Basal Side of the Columnar and Cubic Ameloblastic Cells. Figure 5b: Central Closely Packed Malignant Neoplastic Cells with Slight and Cytoplasmic Claudin-1 Expression. Figure 5c: Two groups of Malignant Cells with Moderate (Left) and Slight (Right) Positivity are Clearly Distinguished. d) Numerous Tumoral Cells with Intensely Stained Nuclei were seen within the Neoplasm. Figure 5d: A Continuous Line of Flat Basal and Parabasal Cells with strong Cytoplasmic Claudin-1 positivity. Several Necrotic Capillaries and Numerous Multinucleated Giant Cells showing Strong Cytoplasmic Claudin Positivity. Figure 5e: Strong Claudin-1 Positive Rim of Endothelial Cells in Extratumoral Blood Vessels. Figure 5f: Claudin Immunoexpression is similar in all types of Malignant Cells.

Many PCNA positive cells were observed and this immunoreaction was in columnar and cubic peripheral ameloblastic cells mainly and most of the basal cells in the complex areas were positive. Also, many strongly PCNA stained cells were observed in a similar distribution as it was with H&E strongly stained cell nuclei (Figure 6). PCNA proliferating index was 94.6%.

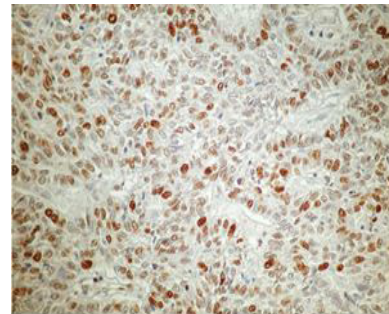


Figure 6: PCNA Immunoexpression in the Basal Ameloblastic cells. Positivity is seen in Basal, Parabasal and Central Cells. Strongly Positive Nuclei are observed in Randomly Located Cells.

Discussion

AC is a malignant odontogenic neoplasm rarely found in the maxillo-mandibular area. In this report, we present an extensive description of the clinicopathological features, H&E microscopic findings of an AC and the first immunohistochemical report of claudins in this kind of neoplasm.

Analyzing this case, we found numerous fusiform, slender cells of scanty cytoplasm and hyperchromatic nuclei evenly distributed through the tumor. Interestingly, this type of cells has been described as diagnostic of the so-called spindle cell variant of the AC, [7], but their impact on biological behavior is still undetermined. Increased number of capillaries in a malignant tumor is a high-risk factor for metastatic disease. In our tumor, we observed that closely packed neoplastic cells in hypercellular areas were associated with numerous blood vessels; however, during five-years duration of the tumor, no metastasis developed. Our findings suggest that the ring of desmoplastic connective tissue enclosing the intratumoral capillaries prevented the intravascular dissemination of malignant cells avoiding metastases. Also, despite we detected malignant neoplastic cells within the adjacent bone, the presence of the thick capsule of fibrous connective tissue avoided the development of metastases, but it did not prevent its invasive behavior.

In this report, we documented the presence of several areas with a complex architecture showing dissolution of the epithelial intercellular cementum, cellular detachment, development of a stellate reticulum-like architecture, and breakdown of the basement membrane with neoplastic cells invading the contiguous connective tissue. Additionally, disintegration of the neighboring connective tissue, increase of the local vascular bed, presence of multinucleated giant cells, and cellular disruption were recorded. These findings strongly suggest enzymatic activity in both compartments epithelial and extra-epithelial, indicative of early events of neoplastic invasion.

Claudins are TJ proteins involved in the process of tumorigenesis in certain types of cancers including oral squamous cell carcinomas [14]. These proteins are related to loss of cell polarity, increase of cellular motility, downregulation of cell-cell adhesion, and reorganization of the cytoskeleton [8-10]. Also, they are involved in recruiting of signaling proteins, cell proliferation and lack of differentiation, cell invasion and survival, local recurrence and both, regional and distant metastases [8-11,15-17]. TJ proteins have been barely studied in odontogenic tumors and their role in the biological behavior of these tumors is poorly understood. The results of two previous studies on ameloblastomas and Keratinizing Cystic Odontogenic Tumors (KCOTs) suggested that their function is to maintain the epithelial cohesion among ameloblastoma cells and their presence reflects the cellular neoplastic nature of KCOTs [12,13].

Claudins 1, 3 and 9 have been identified as important molecules for neoplastic behavior, development of carcinomas and epithelial-mesenchymal transformation promotion [16,18]. Decreased level of claudin-1 has been found in different types of cancers of low metastatic behavior [19,20]. Low immunorexpression of this protein in the analyzed tumor supports its low level of malignancy and its non-metastatic condition. Notwithstanding the existence of closely packed malignant neoplastic cells associated with abundant intratumoral capillary blood vessels, showing discontinuous or absent immunorexpression in the endothelial lining, no metastasis developed. Loss of TJs is frequently seen during cancer progression and claudin translocation to cytoplasm and nucleus has been identified during the epithelial-mesenchymal transformation [18]. Our finding of slight cytoplasmic immunopositivity and heterogenous nuclear immunorexpression found in the closely packed malignant cells correlates with the low degree of differentiation of these cells. Also, we observed that two cellular groups with different intensity of cytoplasmic immunostaining and distinctive degrees of cell differentiation were present in the analyzed tumor. It is well known that poorly-differentiated cells loss their contact inhibition properties and acquire invasive capacities [21]. These results support the aggressive behavior of the studied tumor.

French, et al. [22] showed that phosphorylation modifications of claudin-1 cause its translocation to the cytoplasm and nucleus and that the subcellular localization of claudin1 may dictate the metastatic capacity of melanoma cells. This mislocation of claudin-1 from membrane to cytoplasm could favor oncogenic signals related to the local aggressive behavior observed in the presented case. This is supported by results from other studies reporting that distribution of claudin-1 in the nucleus and cytosol is related to the up-regulation of cell proliferation in several cancers [23,24]. These studies suggested that nuclear location of claudin-1 could be associated with nuclear localization of β -catenin in colon cancer [23] and reduced apoptosis in nasopharyngeal carcinoma cells under drug treatment [24]. Also, increasing of claudin-1 in

the intratumoral neoplastic cells and those invading the neighbor disintegrated connective tissue, suggests that dissolution of the intercellular tissue could be related to claudin-1, increasing and enhancing activation of pro-matrix metalloproteinase-2 [25]. Intense nuclear claudin-1 localization in many neoplastic cells, in cells associated with the stellate reticulum-like areas, and those inside the neighbor connective tissue, reinforces our idea on the role of claudin-1 in the invasive behavior of this neoplasm [16,22].

In our analyzed tumor, negative expression of claudin-1 in the intratumoral blood vessels concurring with the presence of a sclerotic collagenous rim in these structures, suggested an altered angiogenic process. In contrast, the extratumoral blood vessels showed strong claudin-1 staining. This finding suggests that as it was demonstrated in other neoplasms, in the analyzed tumor the angiogenic process may be additionally regulated by other growth factors as the VEGF [26].

Claudins -3 and -9 are associated with promotion of the epithelial-mesenchymal transition, increased cellular growth rate, migration, invasion, and metastases [27-29] and it has been reported that down regulation of both proteins could reduce these functions [30,31]. The negative immunorexpression of claudins -3 and -9 could explain the lack of metastases in the studied AC. Unfortunately, most of the direct or indirect molecular mechanisms underlying the changes in the expression levels of claudins remain unknown.

PCNA is a nuclear non-histone protein essential for synthesis of DNA and is an accessory protein for DNA polymerase alpha activity. This enzyme rises during the G1/S phase of the cell cycle, and non-proliferating cells as quiescent and senescent cells have very low levels of PCNA mRNA [32]. When cells are in proliferating phase, they remain a longer time in the G1/S phase, and for this reason, PCNA expression may be used as a marker of cell proliferation. Additionally, this protein has an essential role in nucleic acid metabolism and it is a component of the DNA replication and repair system [33]. PCNA was rarely determined in AC and as it was in our case, other researchers found a remarkably high PCNA index [34-36]. Bologna-Molina, et al. found that PCNA index was significantly different comparing benign ameloblastomas and AC, confirming the biological behavior of this malignant neoplasm. Our findings and those previously published [34-36], suggest that PCNA index is associated with malignant behavior in AC.

The findings of increased immunorexpression of claudin-1 in the whole tumoral cells especially in the ameloblastic columnar basal and parabasal cells strongly suggest that invasive properties are associated to them and support the theory that functions of claudins are highly tissue-specific and may depend on the cell type and the stage of the studied tumor. Also, the positive immunorexpression of PCNA in these cells suggests that the main front of invasiveness is related to them. Additional studies are needed to

evaluate the involvement of claudins and other TJ molecules in the biological behavior of AC.

Acknowledgements

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