Enigma of CD56 and S100 positive-high-grade undifferentiated malignant tumor of uncertain histogenesis of the mandible – A rare case report

Venkatesh Anehosur¹, Prashant Lowell Monis¹, Abhijit Joshi¹, Adithi Bhat¹, Niranjan Kumar²

¹Department of Oral and Maxillofacial Surgery, SDM Craniofacial Surgery and Research Centre, SDM College of Dental Science and Hospital, Shri Dharmasthala Manjunatheshwara University, Dharwad, Karnataka, India, ²Department of Plastic and Reconstructive Surgery, SDM Craniofacial Centre, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India

Abstract

Purpose: The purpose of this study was to highlight difficulty index in diagnosing and treating an aggressive and infiltrative malignancy in a young patient.

Material: Undifferentiated tumors represent either as a primary neoplastic lesion showing no differentiation or as a metastatic deposit of an unknown primary neoplasm without obvious cell line of differentiation. These tumors are rare and pose a challenge to the diagnosis and treatment outcome. This rare case report is of a young female presenting with an aggressive osteolytic left mandible body pathology. Pre-operative incisional biopsy and post-operative excisional biopsy were subjected to histopathology and immunohistochemical analysis. None of the cellular level diagnostic modalities yielded a definitive diagnosis. The patient was subjected for aggressive resection based on the clinical and imaging findings. Conclusion: From the date of patient presentation to 2 years of follow-up with two surgeries, the concluding histopathology diagnosis was not established. In spite of recent advances in diagnosing, imaging modalities, it is difficult to establish a treatment protocol for disease free survival. It is more agonizing to see a young patient undergoing so much scrutiny with limitations in all advanced medical technology. In such cases wherein definitive diagnosis cannot be achieved despite a thorough cellular level examination, the treatment solely depends on the clinical features of presenting signs and symptoms of the patient.

Keywords: Angiosarcoma, free fibula flap, immunohistochemistry, segmental resection, tumor marker

Introduction

Undifferentiated tumors are those which on light microscopy morphology show little or no evidence of differentiation.¹ Undifferentiated tumors account for 1.1% of all tumors diagnosed in the head and neck region.² These tumors pose challenge to both the pathologist and the surgeon as there exists no defined treatment modality for their management.

Case Report

An 18-year-old female visited us complaining of pain and swelling on her lower left jaw since 45 days. She gave history of extraction of a mobile mandibular left molar with a private dentist prior to this. Post-extraction ordeal consisted of dull continuous pain which disturbed her sleep. Diffused extraoral swelling which was evident 5 days post-extraction and which did not respond to antibiotics or anti-inflammatory medications.

On reporting with a referral to our craniofacial unit, the patient had a diffused extraoral swelling on to the left mandibular body region. It was tender, non-compressible, and firm in consistency with no local rise in temperature. The left submandibular lymph nodes were enlarged, mobile, and non-tender. Intraorally, a proliferative growth was noted in region of missing lower left first molar mimicking similar to an infected socket. It measured approximately 4 × 3 cm and occupied the left buccal vestibule. Buccolingually, lesion extended from posterior left buccal vestibule to the left posterior alveolar ridge. There was no extension into the floor of the mouth [Figure 1]. On palpation, the lesion was soft in consistency, coarse in texture, and non-tender, and induration of surrounding tissues was present, with no evidence of discharge or bleeding on probing.

Orthopantogram [Figure 2] and computed tomography scan revealed an osteolytic lesion occupying the entire mandibular body and completely destroying the buccolingual cortices,
sparing 3 mm of lower border of the mandible. Mandibular left first and second molar were missing. An impacted third molar was noted partially within the radiolucency. The borders of the radiolucency were rough, irregular, and scalloped. There was no radiograph available before extraction which might have added importance to the context. Values of routine blood investigation were within normal limits. Findings were suggestive of rapidly progressive lesion which was explained to the patient’s parents and consented for an incisional biopsy of the lesion under local anesthesia.

Histopathology revealed, polygonal cells with large hyperchromatic nuclei and scant eosinophilic cytoplasm. Cells were mainly epithelioid admixed with spindloid cells. Tumor cells were surrounded by interconnected vascular channels and clogged with red blood cells. Multinucleated cells and mitotic figures were seen. Areas of necrosis, hemorrhage, and exudate were seen. The histopathology was suggestive of angiosarcoma. Immunohistochemistry (IHC) was done for the confirmation same. IHC revealed tumor cells positive for CD56 and focally for S100. The tumor was negative for AE1/AE3, CK, EMA, LCA, CD3, CD20, CD79, CD4, CD 23Desmin, Mic2, Ckit, CD31, CD34, synaptophysin, chromogranin, TF1, and CD23. IHC revealed poorly differentiated malignant tumor and, hence, was noncontributory.

High-resolution ultrasonography (Philips HD 11) of left cheek revealed, intramedullary soft-tissue expansile lesion with gross cortical destruction, and exaggerated flow signals indicative of benignity than malignancy. Isolated left submandibular reactive lymph node enlargement was noted.

CT
Angiography (Siemens somatom), plain, and contrast-enhanced revealed, expansile osteolytic lesion involving the middle, and posterior thirds of mandibular body measuring: 35 mm (anteroposterior) × 32 mm (mediolateral) × 25 mm (craniocaudal) [Figure 5]. Feeding vessel to the lesion was a branch of lingual artery. The lesion showed intense enhancement (NCET 60–80 HU and CECT 180- 200 HU) on post-contrast study in arterial and venous phases, suggestive of a vascular tumor [Figure 4]. There was expansion of inferior alveolar canal and bilateral enlargement of level IB group of lymph nodes.

Chest X-ray and ultrasonography of pelvis and abdomen revealed, no detectable metastatic lesion, and cancer of unknown primary origin was ruled out.

Considering factors such as young age of the patient, aggressive, fast growing, and infiltrative nature of the lesion and conflicting opinions of pathologists, surgical resection was planned and subjecting the entire pathology for evaluation. Segmental mandibulectomy with safe margins of 2 cm on either side was done by first adapting the template and pre-bending the reconstruction plate 2.4 mm, and fixation done with three screws on either side. Without removing, the resection plate osteotomy cuts were marked and oscillating saw was used to complete the osteotomy cuts. Entire lesion was delivered out in toto without disturbing the reconstruction plate [Figure 3]. The tumor margins and Level I, II, and III lymph nodes which were suspicious were sent for frozen sections and all the margins were reported negative. Mandibular reconstruction using reconstruction plate was to maintain the mandibular continuity and with an intent for secondary reconstruction using a free fibula flap at a later stage once the histopathology and tumor biology that were confirmed.

From the main specimen, the pathologist confirmed the presence of malignant tumor cells arranged in a sheet such as pattern traversed by delicate vasculature. Frank epithelioid, osteoid/chondroid/neuroblastic, and rhabdomyoblastic differentiation were not seen. Impression was that of a high-grade undifferentiated malignant tumor of uncertain histogenesis [Figure 4]. The surgical margins for both soft- and hard-tissue was negative.

IHC revealed tumor cells expressing SMA, S-100 protein focally, and immunonegative for cytokeratin, EMA, Mic 2, bcl 2, ERG, Desmin, and CD 34. On histology and IHC, it was not possible to determine whether the lesion was a carcinoma, melanoma, or a sarcoma.
The patient was followed up on a regular basis for 18 months with a disease-free status. At 20 months post-operative follow-up, the patient reported with fractured reconstruction plate at the angle region. Radiographs and CT were done to rule out local recurrence. Microsurgical free fibula flap transfer was done to reconstruct the mandibular continuity defect. Surgical exposure of the neck for the vessels to anastomosis revealed suspicious enlarged lymph nodes at Level IIa region which was subjected for histopathology. Level IIa node confirmed the evidence of intravascular tumor emboli. Post-operatively, the healing was uneventful. Post-operative full body PET scan revealed no obvious metabolically active recurrent lesion or metastatic deposit. The patient was advised to undergo Intensity-Modulated Radiation Therapy by the oncologist, but the patient denied any further treatment despite the strong advice. At 2 years 4 months post-operative follow-up, the patient reported back with swelling over entire left half of the face. The orthopantogram revealed condylar stump resorption. CT (plain and contrast) revealed erosion of the left pterygoid plates, posterior wall of maxillary sinus, ramus, and condylar process of the mandible [Figure 6] and severely compressed internal jugular vein and carotid with partial intraluminal defects, suggestive of recurrence. The patient was lost for follow-up thereafter.

**Discussion**

Undifferentiated tumors represent either as a primary neoplastic lesion showing no differentiation or as a metastatic deposit of an unknown primary neoplasm without obvious cell line of differentiation. Clinically, undifferentiated tumors tend to be

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**Figure 3:** Surgical resection with 2 cms bone margin with reconstruction plate *in situ*

**Figure 4:** Polygonal cells with large hyperchromatic nuclei and scant eosinophilic cytoplasm (X40)

**Figure 5:** 3D computed tomographic angiography scan showing expansile osteolytic lesion showing intense enhancement on post contrast study in arterial and venous phases

**Figure 6:** Axial computed tomographic scan (plain and contrast) exhibiting large soft tissue density heterogeneously enhancing mass lesion in the masticator space with erosion of condylar, coronoid and ramus of mandible on left side
highly malignant, aggressive, usually fatal and unresponsive to all attempts rendered for disease control.\(^1\) It has an increased prevalence in the seventh decade of life.\(^2\) Undifferentiated tumors account for 1.1% of all tumors diagnosed in the head and neck region and shows the following order of site predilection; lymph nodes – 20.9%, pharynx and neck – 16.3%, paranasal sinus – 14%, nose – 11.6%, oral cavity – 4% followed by ear, skin, and larynx.\(^2\) Since these neoplastic cells lack morphologic differentiation diagnosis and classification by histopathology is extremely difficult. In such cases, immunohistochemical analysis aids as a powerful complementary tool. Lesions that pose challenge to diagnose through routine microscopy can be accurately classified by immunohistochemistry.\(^3\) However, in this case, both histopathology and IHC were noncontributory. Moreover, there are very few references in the literature, wherein IHC analysis for identification of undifferentiated tumors of head and neck is done.\(^2\) For treatment purposes, it is very important to understand the nature of the lesion as in whether it is epithelial, mesenchymal, or hematopoietic.\(^1\) In our case, it was not possible to determine whether the lesion was a carcinoma, sarcoma, or melanoma. Another contradiction existed between the imaging modalities and microscopy analysis. Both HRUSG of the lesion and computed angiography of the face were suggestive the lesion to be vascular, but this was disproven by histopathology and IHC.

On IHC, the tumor was positive for CD56 marker and focally positive for S100. Both these markers are not specific. Few lesions which are positive for CD56 and S100 markers and applicable to head and neck pathology include osteosarcoma, rhabdomyosarcoma, desmoplastic small cell tumor, schwannoma, meningioma, glial tumors such as schwannoma, neurofibroma, benign and malignant melanocytic tumors, granular cell tumor, and myoepithelial tumors.\(^1\) The pathologist ruled all of the lesions mentioned.

There were no evidence-based studies to state whether the lesion was radiosensitive or radioresistant.

Since there was no precise diagnosis, there was no established algorithm required for treatment management. Unlike routine cases, a delayed reconstruction was advocated for this particular case. This was done because immediate reconstruction would cover the mandibular defect site, decreasing the ability to detect recurrence. To prevent recurrence, the surgical margins need to be cleared completely off the lesional tissue by means of permanent sectioning in order to achieve a successful reconstruction. Frozen sections are fairly reliable for soft tissues, but they are less suitable for mandibular margins.\(^3\) Reconstruction was done with free fibula flap as it offers adequate bone stock which is optimum for osseointegrated dental implant fixation.

**Conclusion**

To conclude, we present a rare case which will add to the literature involving a young patient with an aggressive lesion which was challenging for both the surgeon and pathologist. In cases wherein definitive diagnosis cannot be achieved despite a thorough cellular level examination, the treatment solely depends on the clinical features of presenting signs and symptoms of the patient. As in this case, we were not able conclude the cause for recurrence even though the approach was aggressive surgery with adjuvant treatment. Thus, more research activity at cellular and molecular biology is essential to understand such rare aggressive pathologies in young patients and all such rare variants should be reported so as to draft an algorithm for management.

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