Editorial

Dedifferentiation in Malignant Salivary Gland Neoplasms: A Critical Appraisal

Several authors have reported cases with focal or diffuse areas of undifferentiated or poorly-differentiated tumor alongside relatively low grade well-differentiated tumor. Such presentations were referred to as 'dedifferentiation', in which the tumor exhibits cellular features of both low and high grades.[1-4] These tumors were suspected to be hybrid tumors arising from the same progenitor cells. Hybrid tumor, by definition, must arise in the same topographical area and must represent histologically distinct tumor entities. Such tumors have to be segregated from dedifferentiated tumors, due to the poorer prognosis of the latter. Dahlin and Beabout[1] were the first to propose the concept of dedifferentiation. They noticed a well-differentiated chondrosarcoma juxtaposed with a poorly differentiated sarcoma. Among the 370 chondrosarcomas cases, dedifferentiation was noticed in 33 cases[2]. Though some authors believe that inadequate removal of the primary tumor could have been a triggering factor for dedifferentiation, Dahlin and Beabout[1] proposed dedifferentiation to be part of normal evolution of the tumor. Although the terminology 'dedifferentiation' sounds optimal in case of sarcomas, its use in epithelial malignancy is questionable. Dedifferentiated epithelial tumors, especially salivary gland neoplasms, exhibit low grade tumor; occurring concurrently with a less differentiated but histopathologically similar counterparts. Seethala et al[4] suggested the usage of the term high grade transformation (HGT), as it better suits the progressive nature of the tumor. In most of the cases, a transitional zone of intermediate grade is noticed between the transformed and the well-differentiated component. This arrangement suggests a common origin for both the components.

The debate as to whether the transformed entity developed as a result of dedifferentiation of the low grade component, or that the stem cells responsible for the formation of the low grade tumor failed to differentiate presenting as poorly or undifferentiated tumor, needs further appraisal. Stanley et al[5] reported the first case of dedifferentiated acinic cell carcinoma (AcCC) in the parotid gland. Till date, more than 50 cases of dedifferentiated or HG (high grade)-AcCC have been reported. In most cases, the dedifferentiated component is represented by anaplastic cells in a solid growth pattern, with multiple mitotic figures and pleomorphism. Comedo necrosis, a salient feature of high grade carcinomas like salivary duct carcinoma, is often noticed. Dedifferentiated AcCC has a considerably poorer prognosis than conventional AcCC, with higher propensity for vascular, perineural and lymph node metastases (50%). The dedifferentiated component is devoid of any acinar cell differentiation and most cases exhibit DNA aneuploidy in contrary to diploid DNA in conventional AcCC.[2,3]

More than 40 cases of dedifferentiated adenoid cystic carcinoma (AdCC) have been reported till date. In addition to these, there have been several reports of hybrid AdCC occurring with high grade carcinoma like salivary duct carcinoma. Most authors regard these hybrid tumors to represent dedifferentiated AdCC. The high grade or the dedifferentiated component consists of poorly differentiated adenocarcinomas or undifferentiated carcinomas. Among the histological subtypes of AdCC, the solid variants carry the worst prognosis as compared to the tubular and cribriform variants.[3,4,6] The dedifferentiated AdCC carries a worsen prognosis than the solid variant of AdCC, with higher propensity for regional metastasis (57%) as compared to conventional AdCC (5 to 25%).[4] Presence of comedo necrosis, microcalcification and pleomorphic cells with open phase nuclei aids in differentiating HG-AdCC from solid AdCC with basaloid cells and hyperchromatic nuclei.[3]

HG-AdCC carries an overall survival rate of 12 to 36 months, making dedifferentiated AdCC to have the worst prognosis of all salivary gland carcinomas.[4] A typical solid AdCC can be differentiated from HG-AdCC by the presence of intermixed tubular and cribriform component in the former. MYB-NFIB fusion gene has been identified in a subset of HG-AdCC. Its presence can be diagnostic where the histopathological distinction is obscure. In epithelial-myoepithelial carcinoma, both the ductal and the myoepithelial component have shown high grade transformation. Most of the high grade epithelial myoepithelial carcinoma (HGEMC) cases exhibited transformation of the myoepithelial component (myoepithelial anaplasia).[7] This is in contrary to the HG-AdCC, where there is drastic loss of the myoepithelial component in the dedifferentiated portion. Data on HG polymorphous low grade carcinoma are inadequate due to a limited number of recorded cases. Though HGT carries a poorer prognosis than conventional form, there have been no recorded fatalities till date.[8] Few recorded cases of HG myoepithelial carcinoma (MC) have shown polygonal eosinophilic glycogen-rich clear cells in the form of solid nests, representing conventional MC. The HG component consists of pleomorphic spindle cells with atypical mitoses.[3,9]

Till date, only two recorded cases of HG mucoepidermoid carcinoma (MEC) exist. The histopathological features of both the cases showed a low grade MEC with characteristic glandular differentiation with multiple cystic

spaces. The high grade component lacks both the mucous cells and the cystic space. A sarcomatous pattern with severe pleomorphism and necrosis is observed in the HG component. Due to the undifferentiated state, these cases can be identified by the presence of CRTC1-MAML2 fusion gene, specific for MEC.[10,11] Two cases of HG hyalinising clear cell carcinoma have been recorded. Both the cases exhibited distant metastases and the patient survival was reduced to less than one year.[12,13] HGT or differentiation is a rare event in salivary gland neoplasms. The etiology of the transformation is still controversial; with the long-standing nature, recurrent, surgical intervention and radiation proposed as one of several possible triggering factors. Most cases of HGT tumors showed higher propensity for local lymph node metastases than their conventional counterparts. Thus, the presence of the HG component mandates neck dissection as part of the primary surgery, regardless of the histological type.[2,3] Due to the drastic reduction in the patient survival, it is vital that a thorough specimen sampling is carried out to exclude the presence of a HG/dedifferentiated component.

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