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Importance of High Grade Transformation and Translocations in Salivary Gland Neoplasms

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Commentary

The concept of high grade transformation in human neoplasms was introduced in 1971 by the report demonstrating that 33 of 370 cases of well differentiated (low-grade) chondrosarcomas contained areas of a high-grade sarcoma [1]. Currently at least 23 different types of primary salivary carcinomas are recognized, some of low and others of high grade malignancy. During the last decade, it has become apparent that a fair number of conventionally low grade salivary tumours do switch to tumours with much more aggressive biological behaviour. This behaviour is for example reflected by a more anaplastic, high grade histologic appearance of the tumour. The "anaplastic" focus, or foci, may be small but nevertheless command the biological behaviour of the entire neoplasm. We recently reported a review of all published salivary so-called salivary hybrid tumours, i.e. tumours with two histologically distinct components (histologically described and defined in 1996). We found 38 cases in 22 publications, and after thorough studies we concluded that most, if not all, of these hybrid tumours probably were examples of high-grade transformation (HGT) in another (pre)existing neoplasm. These are tumours where one component is of low grade malignancy and the other of high grade, proportion of which may vary, and so may the histology. Sufficient data was not available to draw a conclusion whether these two tumour components had a common molecular pathway or not. Several findings indicated that very likely the mechanism had been a high-grade transformation rather than two different tumours occurring at the same place (still to be separated from so-called collision tumours). During the same period of time (1996-2016) more than a hundred cases of HGT in salivary gland neoplasms had been reported [2]. In another study, we investigated the clinical consequences of HGT in salivary adenoid cystic carcinoma. Conventional adenoid cystic carcinoma is already a tumour of high grade malignancy in the long term (10-20 years) but in cases with HGT their biological behaviour change drastically with early spread to lymph nodes and distant metastasis, and a more dismal short-term prognosis, prompting a more aggressive initial treatment [3]. Similar observations of HGT have been made in acinic cell carcinoma, and in also in salivary polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma, low-grade mucoepidermoid carcinoma, myoepithelial carcinoma, hyalinizing clear cell carcinoma and, mammary analogue secretory carcinoma [4].

The molecular genetic mechanisms responsible for HGT in salivary neoplasms remain largely unknown. Abnormalities of a few genes, such as p53 (loss of heterozygosity at p53 microsatellite loci and p53 gene point mutation), C-MYC (amplification), cyclin D1, HER-2/neu (overexpression), and loss of pRb expression, have been documented. Chromosomal gains confined to areas of HGT of adenoid cystic carcinoma, and losses in conventional areas, have been reported. Oncogenes on chromosome 17q23 appear to be of interest. It has been demonstrated that MYB/NFIB translocation is not necessarily an early event, and possibly not even fundamental for the progression to HGT in e.g. adenoid cystic carcinoma. Studies have shown that HGT is not always accompanied by an accumulation of genetic alterations as both the low and high grade components appear to harbour unique genetic alterations, thus indicating the possibility of parallel progression [5-10]. Apart from the genetic events mentioned here, there are currently five types of salivary tumours known to harbour specific translocations. Identification of these translocations and/or their fusion proteins has shown to be of great diagnostic value. Pleomorphic adenoma/carcinoma ex pleomorphic adenomas have fusion of transcription factor genes *PLAG1* and *HMGA2*. Mucoepidermoid carcinomas have t(11;19) (q21;p13) with fusion genes *CRTC1-MAML2* and adenoid cystic carcinoma t(6;9)(q22-23;p23-24) with fusion genes *MYB-NFIB*. Mammary analogue secretory carcinomas (MASC) have t(12;15) (p13;q25) resulting in *ETV6-NTRK3* gene fusion, and hyalinizing clear cell carcinomas t(12;22)(q13;q12) resulting in *EWSR1-ATF1* gene fusion [11]. The full importance of the translocations in relation to HGT remains unclear and the trigger mechanisms for the translocations are largely unknown.

A recently recognized extremely aggressive human neoplasm, the so-called NUT midline carcinoma (NMC), characteristically locates to the midline of the head and neck, and mediastinum. We reported a series of seven cases of laryngeal NUT carcinoma and six of the patients died within 3 to 11 months [12]. NUT carcinoma is regarded by most as an undifferentiated variant of squamous cell carcinoma but is further characterized by a specific chromosomal translocation, not present in conventional squamous cell carcinoma. NMC has chromosomal rearrangements of the gene encoding nuclear protein in testis, NUT, at 15q14. The *BRD4* (bromodomain containing 4) gene on 19q13 is the most common translocation partner gene to NUT resulting in the t(15;19) (q14;p13) karyotype. The fusion forms a 6.4-kb fusion oncogene, *BRD4-NUT*. Albeit very speculative, it may be possible that the occurrence of this translocation could represent a high-grade transformation in squamous cell carcinoma.

Conclusion

High-grade transformation in salivary gland neoplasms is nowadays a well-recognized event and that requires meticulous histological examination of the surgical specimen. It drastically alters the biological behaviour of the tumour, as well as the treatment strategy and the prognosis.

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