The classification of sebaceous tumors has become more complex with time. Sebaceous adenoma, sebaceoma\(^1\), sebaceous epithelioma\(^2,3\), sebaceous carcinoma, superficial epithelioma with sebaceous differentiation\(^4,5\), sebomatricoma\(^6\) (a term proposed to unify the spectrum of benign sebaceous neoplasia) and an interesting spectrum of lesions associated with Muir-Torre syndrome have been described\(^7\). Sebaceous neoplasia can also arise secondarily in the context of nevus sebaceus\(^8-12\). Other cutaneous epithelial and appendageal neoplasms with a significant sebaceous component have been noted including basal cell carcinoma\(^13,14\), trichofolliculoma\(^15\), and microcystic adnexal carcinoma\(^16\). Given the intimate association of pilar and sebaceous units, the association of sebaceous differentiation with tumors showing follicular differentiation is not surprising\(^17\). In the following paragraphs, a simple classification scheme for sebaceous neoplasms will be presented. In addition, the biology of these intriguing neoplasms and their relationship to Muir-Torre syndrome will be briefly discussed.

The most significant clinical differentiation to make in sebaceous neoplasia is between benign and malignant (i.e. sebaceous carcinoma). There are two types of sebaceous carcinoma — periocular and extraocular. Periocular sebaceous carcinoma accounts for approximately three-quarters of cases and is associated with local morbidity and significant mortality upon metastasis\(^14,18\). In
contrast, extraocular sebaceous carcinomas may be considerably less aggressive, but this finding has not been universal and more studies are needed\textsuperscript{14, 18-20}. Occasionally, the diagnosis of periocular sebaceous carcinoma will be required on frozen section and oil red O can be helpful in challenging cases. Alternatively, other recently employed immunohistochemical stains such as adipophilin can be useful in formalin-fixed, paraffin-embedded cases\textsuperscript{21, 22}. It should be noted that benign sebaceous neoplasms are relatively rare in the periocular region (relative to carcinomas) and thus diagnosis of a benign sebaceous tumor at this site should be carefully considered.

Benign sebaceous neoplasms have been more subclassified than their malignant counterparts. However, all benign sebaceous neoplasms share a similar clinical appearance/setting and are typically characterized by a flesh-colored to slightly yellowed papule involving the head and neck region of older individuals. Histologically, benign sebaceous neoplasms form a spectrum of lesions ranging from an organoid appearance with prominent mature sebocytes (classic sebaceous adenoma) to cases with more prominent germinative cells (sebaceoma). All of the other described benign sebaceous lesions appear to fall along this continuum. In recognition of this, the unifying term sebomatricoma was proposed for this family of benign sebaceous neoplasms, but this terminology has not been widely adopted\textsuperscript{6}. Although, different names are helpful for recognizing individual cases as sebaceous neoplasia, there is currently limited evidence of significant biological or clinical relevance. However, more studies and comparisons are needed.

Muir-Torre syndrome (MTS) was described virtually simultaneously in the late 1960's\textsuperscript{23, 24} and is now known to be a subset of the hereditary non-polyposis colorectal carcinoma syndrome (HNPCC)\textsuperscript{25-27}. MTS is the combination of sebaceous neoplasia and internal malignancy with colonic carcinoma being the most common\textsuperscript{28}. The molecular hallmark of this syndrome is microsatellite instability, resulting primarily from loss of the DNA mismatch repair (MMR) genes
MSH2 and MLH1, with the former being much more common in MTS. Microsatellite instability (MSI) can be demonstrated by PCR-based methods and loss of mismatch repair genes can be revealed by immunohistochemistry with excellent sensitivity and specificity. Demonstration of MMR defects by either method suggests the need for a clinical evaluation for MTS and can guide germline testing performed with the guidance of genetic counseling. The accompanying internal carcinomas show a similar molecular signature.

The described array of sebaceous neoplasms seen in the context of MTS includes virtually all of those described above. However, superficial epithelioma with sebaceous differentiation has been only rarely described and its association with MTS is uncertain. Interestingly, non-ocular sebaceous carcinomas encountered outside of the head and neck region are much more commonly associated with loss of MMR proteins and MTS than peri-ocular sebaceous carcinomas. Head and neck non-ocular (and peri-ocular) sebaceous carcinomas very rarely show MMR protein loss and are not commonly associated with MTS. The same trend is true for benign sebaceous lesions, though more than a third of head and neck forms also show MMR loss and are linked to MTS. Importantly, the diagnosis of any cutaneous sebaceous tumor outside of the head and neck region is rare, but when encountered is strongly associated with MMR loss and MTS.

The array of sebaceous neoplasia associated with MTS can show unusual features and resist precise classification. Both cystic features and “keratoacanthoma-like” architecture have been described. Distinguishing benign from malignant forms of MTS-associated sebaceous neoplasia can be challenging given the unusual features sometimes encountered in these tumors. Thus, many recommend conservative complete excision of virtually all sebaceous neoplasms encountered in this setting. This can be somewhat challenging in those forms of MTS that show many sebaceous neoplasms (sometimes more than 100 over a lifetime).
Recent work on skin adnexal developmental pathways has shed insight into the molecular pathogenesis of sebaceous neoplasia. It seems that the balance of the Wnt, hedgehog and c-Myc pathways influences primitive cutaneous stem/precursor cell fate between cutaneous squamous epithelium, follicular and sebaceous fates\textsuperscript{45-47}. Since stem cells are long-lived, they represent a potential compartment for the accumulation of the often multiple genetic mutations required to produce neoplasia and malignant degeneration\textsuperscript{48, 49}. Cells with immunohistochemical markers characteristic of stem cells can be identified in sebaceous neoplasia\textsuperscript{50, 51} and stem-like cells have been isolated from a sebaceous carcinoma cell line (Stephen Lyle, unpublished data). Inactivating mutations in the \textit{LEF1} gene, a downstream effector in the Wnt pathway, have been described in benign sebaceous neoplasia\textsuperscript{52}. These mutations appear to both foster a sebaceous fate and promote tumor development possibly by blocking the induction of p53\textsuperscript{53}. Based on this and other observations, it is now possible to manipulate \textit{in vitro} cutaneous epithelial precursor or stem cells to show sebaceous differentiation\textsuperscript{46, 54}. These findings may shed light on the cancer stem (or progenitor) cell hypothesis and the pathogenesis of sebaceous neoplasia.
Bibliography