Sebaceous neoplasia and the Muir–Torre syndrome: important connections with clinical implications

Sara C Shalin, Stephen Lyle1, Eduardo Calonje2, and Alexander J F Lazar3

Department of Pathology, Baylor College of Medicine, Houston, TX and 1 Department of Cancer Biology, University of Massachusetts Medical Center, Worcester, MA, USA 2 St John’s Institute of Dermatology, St Thomas’ Hospital, London, UK 3 Departments of Pathology and Dermatology, Section of Dermatopathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Abstract

Sebaceous neoplasia comprises a spectrum ranging from benign to malignant. Proper histological identification is important for treatment, prognosis and potential association with the Muir–Torre syndrome (MTS). Our increased understanding of the significance and pathogenesis of these tumours has led to improved risk stratification, screening recommendations, and treatment of patients with an initial presentation of a sebaceous tumour. This review focuses on the diagnostic and histological features of sebaceous lesions, the MTS, and recent insights into the molecular pathogenesis of sebaceous tumorigenesis.

Keywords

mismatch repair deficiency; Muir–Torre syndrome; sebaseoma; sebaceous adenoma; sebaceous carcinoma; sebaceous hyperplasia

Sebaceous glands

Sebaceous glands are associated with the hair follicle, arising at the junction of the inferior portion of the follicle infundibulum and the isthmus. Normal sebaceous glands are composed of lobular acini lined on the periphery by a thin layer of flattened to cuboidal basoloid, or germinative, cells with scant cytoplasm (Figure 1A). The inner portions of sebaceous glands are composed of mature seocytes—cells with a centrally-located, often scalloped or indented nucleus and multivacuolated cytoplasm due to the accumulation of lipid secretions.1 Sebaceous glands, found in higher concentrations on the head and neck region, are responsible for the production of sebum, a lipid-rich secretion with a variety of postulated functions.1 These structures are androgen-sensitive and typically become more prominent during puberty.4 Developing sebaceous glands have been shown to variably express cytokeratin (CK) 15, which marks potential multipotent stem cells of the pilosebaceous unit and more recently has been shown to be present within sebaceous neoplasms as well.5–6

Address for correspondence: Alexander Lazar, MD/PhD, The University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd- Unit 85, Houston, TX 77030-5009, USA. alazar@mdanderson.org.
**Ectopic sebaceous glands**

Although most often associated with hair follicles, ectopic sebaceous glands arising independent of follicular structures are well described. These lesions may arise as small 1–3-mm yellow-to-white papules occurring on mucosal surfaces, namely the lips and genital regions, where they are referred to as Fordyce spots. Similar lesions on the female breast are called Montgomery tubercles. These are common enough at these sites in the population that they can be considered variants of normal. Ectopic sebaceous glands arising in a variety of more unusual locations, including the oesophagus, vagina, cervix, thymus and penis, have been the subject of numerous case reports. These generally appear to be of no consequence.

**Sebaceous hyperplasia**

Sebaceous hyperplasia is the benign overabundance of normal-appearing sebaceous lobules. Clinically, these lesions are small, usually < 5 mm in greatest dimension. They are generally flesh-coloured papules, usually with a central depression or umbilication. Their clinical appearance, along with their predilection for the face, is the basis for periodic clinical confusion with basal cell carcinoma. Histological examination of these lesions reveals superficial sebaceous lobules surrounding a centrally dilated pore or follicular structure, the correlate of the central umbilication (Figure 1B). Sebaceous lobules are increased in number but not dramatically in size, occupy a more superficial position in the dermis, but have only two layers of peripherally located basaloid or germinative cells. Treatment of sebaceous hyperplasia is not required, but may be achieved with conservative excision if it becomes a cosmetic issue or clinically confused with a more concerning lesion.

The development of sebaceous hyperplasia has been associated with immunosuppression, specifically noted to occur in renal transplant patients treated with cyclosporin. Although the pathogenesis of sebaceous hyperplasia is not well understood and its origin as either a reactive or neoplastic process is not well established, possible contributing factors may include androgenic stimulation, ultraviolet radiation, and immunosuppression. Unlike many of the entities discussed subsequently, sebaceous hyperplasia does not appear to be definitively linked to Muir–Torre syndrome (MTS). Deficits in mismatch repair genes, a frequent finding in cases of MTS, are generally not identified in cases of sebaceous hyperplasia. Case reports documenting an association between sebaceous hyperplasia and internal malignancy are found within the literature; however, these reports may simply reflect the underlying frequency of this diagnosis within the general population.

**Sebaceous adenoma**

Sebaceous adenomas are benign sebaceous tumours that clinically appear as tan, pink, or yellow nodules or papules, usually about 5 mm in greatest dimension. Like most sebaceous proliferations, these tumours typically arise on the head and neck regions of older individuals, although occurrence in many other locations has been documented. Sebaceous adenomas maintain a lobular and organoid architecture, and often show connection with or replacement of the overlying squamous epithelium (Figure 2A). There is an expansion and increased prominence of the peripherally located basaloid cells compared with sebaceous hyperplasia (Figure 2). This increase in the number of germinative cells is a key discriminator between the categories of sebaceous hyperplasia and sebaceous adenomas or sebaceomas. Sebaceous adenomas show variably expanded basaloid cells, with more than the normal two cell layers seen in normal sebaceous glands and sebaceous hyperplasia, but by convention are < 50% of the tumour cell volume (> 50% basaloid cell content is seen in sebaceoma). Sebaceous adenomas thus also maintain a prominent population of mature sebocytes often concentrated in the central portion of the neoplasm,
making their sebaceous differentiation conspicuous in most cases and imparting an organoid quality to the tumour. Noticeable cytological atypia or significantly increased mitotic rate should prompt a re-evaluation of the diagnosis, as these features are generally minimal.23–25 These tumours are well circumscribed and often lobular.

Clinically, sebaceous adenomas may be mistaken for basal cell carcinoma. Histologically, the differential diagnosis of sebaceous adenoma includes other lesions with clear cytoplasm, including clear cell variations of eccrine, melanocytic, keratinocytic or xanthomatous lesions, as well as metastatic lesions such as renal cell carcinoma, or perhaps other lesions with sebaceous differentiation. The characteristic bubbly or multivacuolated cytoplasm and crenated nuclei of mature sebocytes coupled with the germinative cells should be helpful features on histological examination (Figure 2D), but immunohistochemical staining may be helpful for particularly difficult lesions (further discussion below).

Sebaceous adenomas are felt to be benign lesions, yet common practice is complete extirpation by conservative excision. The established association between the presence of sebaceous adenomas and MTS deserves reference within issued pathology reports so that patients can be appropriately evaluated for possible additional syndrome findings as discussed further below.

Sebaceoma

Clinically, sebaceomas appear similar to sebaceous adenomas, although perhaps slightly larger in size, ranging from 5 to 30 mm in greatest diameter with a fleshy yellow to orange colour. Similar to other sebaceous tumours, these lesions typically arise in the head and neck region.26–27

The histology of sebaceoma differs from that of sebaceous adenoma in that the germinative, basaloid cells predominate over the mature sebocytes, with > 50% of the tumour cells being basaloid (Figure 3). Furthermore, sebaceomas typically lose the organoid quality seen in sebaceous adenomas, resulting in a seemingly haphazard placement of mature sebocytes without the sense of central maturation usually encountered in adenomas. Mature sebocytes may be focal and scarce (Figure 3B). Sebaceomas can rest entirely within the dermis or display overlying connection to the epidermis. Ductal structures and squamous differentiation may also be present.28 Despite the loss of organoid quality, these lesions generally maintain circumscription and symmetry.28 Mitotic figures may be present within the basaloid cells, but the lesions maintain an overall well-circumscribed architecture without significant cytological atypia. More recently, cytological atypia and mitoses, including atypical forms, have been suggested to occur rarely in sebaceous neoplasms that are otherwise characteristic of benign sebaceomas, although this has been accompanied with controversy.24–25 Of note, sebaceomas (and sebaceous lesions in general) do not display peripheral pallisading of basaloid nuclei or the retraction from the surrounding stroma that is present in basal cell carcinomas, which may aid in distinguishing these lesions.27–29 Additionally, various histological patterns have been described within the spectrum of sebaceomas, including carcinoid-like, rippled and reticulated patterns.30–32

Sebaceomas are generally treated by conservative excision. Like sebaceous adenomas, sebaceomas are considered part of the spectrum of MTS. Clinically and histologically, sebaceomas have overlap with sebaceous adenomas and together form the benign end of the spectrum of sebaceous neoplasia associated with the MTS. While the many similarities between these two tumours suggest that they could be conceptualized as a continuum of sebaceous neoplasia, it is appropriate to distinguish sebaceoma because the higher basaloid content can cause confusion with non-sebaceous tumours such as basal cell carcinoma and also sebaceous carcinoma.
Other sebaceous lesions and terminology

Numerous additional terms have been introduced into the literature, which may encompass the various sebaceous neoplasms. These terms, including “sebaceous epithelioma” and “sebomatricoma”, have variably included sebaceous adenomas, sebaceomas, and non-sebaceous tumours such as basal cell carcinoma with sebaceous differentiation. In addition to a lack of well-defined diagnostic features for these lesions, there has also been disagreement and confusion regarding malignant potential, particularly in the case of the sebaceous epithelioma. Furthermore, these broad terms do not clearly distinguish the sebaceous tumours most likely to be associated with the MTS. These terms do have some limited degree of support within the literature, but the terms sebaceous adenoma and sebaceoma as defined above will encompass the vast majority of benign sebaceous lesions encountered, although the histological spectrum certainly admits to variation. Conceptually, one could certainly view sebaceomas as “cellular” sebaceous adenomas given their similar clinical contexts and significance. However, sebaceoma is a well-defined entity and it recognizes lesions with prominent basaloid features and sometimes more prominent mitoses as benign and markers of the MTS.

Other rare sebaceous neoplasms include superficial epithelioma with sebaceous differentiation and mantleoma. Superficial epithelioma with sebaceous differentiation is rarely described, but a recent report suggests that it may be more common than previously thought. It is a benign entity composed of a plate-like epidermal growth with thickened, anastamosing rete ridges and interposing lobules of basaloid cells and mature sebocytes. Mantleoma is described as a benign folliculocentric tumour with sebaceous differentiation that is thought to replicate the follicular mantle. Fibrofolliculomas and trichodiscomas, benign tumours seen in Birt–Hogg–Dube syndrome, are considered by some to show mantle differentiation as well, and may represent overlap with mantleoma. Perhaps due to their rarity, neither superficial epithelioma with sebaceous differentiation nor mantleoma has a well-defined relationship with MTS, although one patient with superficial epithelioma with sebaceous differentiation reported an internal malignancy.

Sebaceous carcinoma

Sebaceous carcinomas are traditionally segregated into two categories: periocular and extraocular. The distinction is important, as malignant sebaceous tumours are more likely to occur in the periocular region (as opposed to adenomas or sebaceomas), and these appear to be less often associated with MTS than their extraocular counterparts.

Periocular sebaceous carcinoma

Sebaceous carcinomas of the periocular region can arise from the meibomian glands, the glands of Zeis, or sebaceous glands of the eyelid. These tumours comprise approximately three-quarters of all sebaceous carcinomas, arising between the sixth and eighth decades of life with an equal gender distribution in the contemporary literature. They are the second or third most common eyelid malignancies after basal cell carcinoma (and squamous cell carcinoma), depending on the published series. A recent large retrospective study on the epidemiological factors of sebaceous carcinoma noted a decreased incidence in persons with black skin. Clinically, sebaceous carcinoma may appear as a painless, rounded nodule, more often on the upper eyelid and usually without ulceration (Figure 4A). Periocular sebaceous carcinoma may be mistaken clinically for an inflammatory condition such as chalazion or blepharoconjunctivitis, resulting in delay in diagnosis. Misdiagnosis as a more indolent malignancy such as squamous or basal cell carcinoma can lead to suboptimal initial clinical management.
the possibility of a sebaceous carcinoma.42 Metastatic spread to lymph nodes is not uncommon, and mortality has been reported up to 20%.48 More recent retrospective studies indicate considerably lower mortality, perhaps owing to earlier recognition allowing application of more effective local excision.41, 42

Histologically, periorcular sebaceous carcinomas often demonstrate an infiltrative architectural pattern within the dermis and extension into the superficial skeletal muscle and subcutis of the eyelid. The tumour cells are enlarged and sometimes pleomorphic basaloid cells with hyperchromatic nuclei and frequent mitotic figures, some of which may be atypical (Figure 4). Depending on the degree of differentiation, sebaceous carcinomas may show obvious or only focal mature sebocytes.49 Intraepithelial or pagetoid spread is a frequent feature that is rarely encountered in extraocular cases (Figure 4C). In interpreting small biopsy specimens, it should be noted that benign sebaceous neoplasms are not common in the periorcular region, and the identification of sebaceous differentiation in such a lesion should prompt strong consideration of malignancy.26

**Extraocular sebaceous carcinoma**

Extraocular sebaceous carcinoma is less common than its periorcular counterpart, generally still arising in the head and neck region, although other sites, including the nipple, thorax, back, and penis, have been reported.41-50-52 Like periorcular sebaceous carcinoma, extraocular carcinoma can be an aggressive malignancy, with varying reports as to the incidence of metastasis and mortality.23, 41-52 The rarity of this tumour and likely referral bias in published series has complicated assignment of the aggressiveness of this tumour.

Clinically, these lesions may be similar to the periorcular carcinomas, presenting as an erythematous nodule or papule with or without ulceration. While many of these lesions have both poorly circumscribed architecture and significant atypia, including pleomorphic, enlarged basaloid cells, frequent and atypical mitoses, and foci of necrosis, some lesions display only one or the other feature (Figure 5A). The presence of either an infiltrative growth pattern or extreme cytological atypia should prompt the diagnosis of malignancy.24-26 Mature sebocytes may be only focally noted and the nuclei often lack the distinctly crenulated features seen in mature sebocytes (Figure 5B, compare with Figure 1A). Unlike periocular disease, pagetoid spread is rare in extraocular sebaceous carcinomas.

Sebaceous carcinomas have been treated with a wide-ranging spectrum of treatment modalities, including wide excision, adjunctive radiotherapy, and even orbital exenteration.41-42 More recently, Moh’s microsurgery has been performed on periocular sebaceous carcinomas with the purported advantage of normal tissue sparing and apparently favourable outcomes, although longer follow-up is needed.47

**The use of immunohistochemistry in sebaceous neoplasia**

Although the identification of unequivocal sebaceous differentiation on routine histological examination alone will usually suffice, there are certain circumstances when the use of immunohistochemistry may facilitate diagnosis. Several readily available immunohistochemical stains, although non-specific, may also be helpful in the determination of sebaceous origin. The mature sebocytes are positive for epithelial membrane antigen (EMA) and negative for carcinoembryonic antigen. CK7 is generally positive in the basaloid cells of sebaceous tumours.5-53

Sebaceous tumours, because of their intracytoplasmic lipid content, will stain with Oil Red O; however, application requires frozen tissue, as standard histological processing eliminates lipid content.26 This stain can be rapidly performed on perioperative frozen
sections. More recently, the use of adipophilin, a protein associated with lipid vesicles, has been described as useful in the identification of sebaceous differentiation54–56 (Figure 6). Because of the contribution of androgen hormones to the activation of sebaceous glands, immunostaining against the androgen receptor has also been reported as a method to determine sebaceous differentiation.4 This stain may be particularly helpful in poorly differentiated sebaceous carcinomas, which may lack staining for EMA and other markers, but additional demonstrations of specificity are needed.4

Though few well-documented cases exist, basal cell carcinomas with sebaceous differentiation frequently enter the differential diagnosis of sebaceous neoplasms, particularly sebaceoma.29 Although the histological processing artefact of tumour retraction from fibromyxoid stroma also indicates basal cell carcinoma, several immunostains have been proposed to aid in differentiating these lesions. The use of EMA and Ber-EP4 immunostaining was investigated and found to be useful in the distinction between these lesions. Nodular-type basal cell carcinomas were typically moderately or strongly positive for Ber-EP4 and sebaceomas were almost always negative for this marker, while EMA staining shows the opposite pattern of reactivity.57–58 Podoplanin (D2-40) is typically weakly and focally positive at most in basal cell carcinomas but positive in sebaceous lesions, particularly sebaceoma.59 CK19 has also been reported to be useful in distinguishing these lesions, with basal cell carcinomas more often displaying strong positivity, whereas sebaceous lesions display only focal immunopositivity.60 Most of the studies supporting these stains are small, and multiple stains should be used in a panel to support rather than overrule the initial histological impression.

Within the spectrum of sebaceous tumours, tumorigenic and proliferative immunomarkers may help if the malignant potential of a lesion is unclear, although histological examination is the best standard for this determination. One study has shown that sebaceous hyperplasia, sebaceous adenomas, and sebaceomas tended to show low levels of p53 and Ki67 (Mib-1) positivity, while sebaceous carcinomas tended to show higher levels of nuclear p53 expression and Ki67 positivity, as well as decreased Bcl-2 expression 61. Podoplanin (D2-40) has also been suggested as a possible marker to distinguish benign from malignant sebaceous tumours. Sebaceomas were found to be immunopositive for podoplanin in basaloid cells. In contrast, most carcinomas tended to be either negative or only focally positive, although some basaloid sebaceous carcinomas were immunopositive.59

Muir–Torre syndrome and sebaceous neoplasia

MTS refers to the independent descriptions made more than four decades ago by Drs Muir and Torre of sebaceous neoplasms occurring coincident with internal malignancy. We now understand this syndrome to represent a subset of the hereditary non-polyposis colorectal carcinoma (HNPCC) syndrome. HNPCC is an autosomal dominant cancer predisposition syndrome due to inheritance of a defective gene encoding a DNA mismatch repair protein. Loss of wild-type allele leads to genomic microsatellite instability (MSI).62–63 Although initially reported having a predisposition solely to colorectal cancer, these patients actually show an increased risk of various malignancies, including endometrial, ovarian, genitourinary, and small bowel cancers. Multiple primary tumours are common, and patients typically present at earlier age with malignancy.62 Many of these patients demonstrate germ-line mutations in genes encoding DNA mismatch repair proteins MLH1 or MSH2 and, less commonly, MSH6, MSH3, MLH3, PMS1 and PMS2. These proteins function to detect and repair errors in base pairing occurring during DNA replication, especially in regions of DNA (microsatellites) characterized by repetitive mono- or dinucleotide repeats. Consistent with the Knudson hypothesis, mismatch repair protein mutation, when paired with a second somatic mutational “hit” of the remaining functional allele, leads to susceptibility to tumour
formation through the accumulation of base pair mismatches and increasing genomic stability.64 The “second hit” may be through somatic mutation or methylation suppression,65 although a small report has suggested that loss of heterozygosity by complete allele loss is unlikely to be a common mechanism.66 Conceptually, mismatch repair genes can be considered tumour suppressor genes.

MTS comprises a small subset (1–3%) of HNPCC families and is characterized by sebaceous tumours or perhaps keratoacanthomas preceding or existing coincidently with visceral malignancies.67 Because the sebaceous lesions may be the presenting feature of a patient with MTS, increasing reports are being published regarding recommendations for patient screening following the diagnosis of a sebaceous tumour.17· 68· 71· 72 The diagnosis of a sebaceous neoplasm should prompt additional clinical and/or laboratory screening, and a currently accepted method to evaluate for the functional status of mismatch repair proteins within the sebaceous tumour is the use of immunohistochemistry with antibodies against the commonly encountered lost mismatch repair proteins, MSH2 and MLH1, sometimes with MSH6 as well.17· 68· 72 (Figure 7). A lack of nuclear immunoactivity within tumour cells is supportive of a mutation in the gene and has been shown to correlate well with high levels of MSI, as assessed by the gold standard of polymerase chain reaction-based amplification and chromatographic or electrophoretic assessment of multiple, defined microsatellite regions of DNA.73· 74· 75 (Figure 8).

Although all types of sebaceous neoplasms (with the exception of strictly defined sebaceous hyperplasia) have been the subject of reports linking them to MTS,77· 78· 80 more recent literature has attempted to better define a genotype–phenotype correlation of the syndrome by confirming the presence of mutations in mismatch repair gene or loss of the encoded proteins within sebaceous neoplasms. Interestingly, in contrast to the colorectal carcinomas of HNPCC, the sebaceous neoplasms implicated in MTS more often display loss of MSH2 much more commonly than MLH1.17· 71· 81· 82 Isolated mutations in MSH6 are noted exceptionally,82 but MTS has not yet been linked to isolated loss of MSH3 or PMS1. Only a subset of sebaceous neoplasms demonstrate evidence of mismatch repair deficiency determined by various tests, ranging from 26 to 59% overall with obvious referral bias in the published series.17· 71· 72 Interestingly, benign sebaceous lesions (sebaceous adenomas and sebaceomas) have been shown to have significantly higher rates of mutations than carcinomas—either extraocular or periocular.17· 18· 82 Moreover, several reports have now documented that loss of mismatch repair proteins is more common in sebaceous tumours occurring outside of the head and neck region and may more strongly suggest MTS.17· 18· 71 Strong indicators of MTS include multiple sebaceous neoplasms, but only a single cutaneous tumour can herald the syndrome. Alternative mechanisms of pathogenesis within the spectrum of MTS may exist, since not all patients with sebaceous neoplasia and a characteristic internal malignancy display MSI.

Additional morphological properties have been suggested to correlate with syndrome-associated sebaceous lesions. Keratoacanthoma-like and cystic change had both been proposed as occurring more frequently in MTS-associated sebaceous lesions83· 84 (Figure 9). However, a recent report did not find cystic change to be statistically associated with sebaceous tumours demonstrating loss of mismatch repair protein expression, but additional study is needed.17 More recently, the presence of increased intratumoral lymphocytes has been shown to correlate with MSI, similar to the feature commonly seen in colorectal carcinomas associated with MSI.71· 85

Interestingly, mutations in the genes for mismatch repair proteins may not be the only mechanism by which to obtain an MTS phenotype. Mutations in the gene MYH, inherited in an autosomal recessive manner, result in an attenuated gastrointestinal polyposis phenotype,
with patients showing an increased risk of colorectal carcinoma and other cancers. The protein product of MYH is involved in DNA base excision repair following DNA oxidative damage. Several case reports have now noted the presence of sebaceous neoplasms in patients with MYH-associated polyposis syndrome, and one paper established that these sebaceous lesions did not exhibit MSI.

**Dissecting the molecular pathogenesis of sebaceous tumours**

Efforts to understand the molecular pathogenesis of MTS, sebaceous neoplasia, or cutaneous neoplasms in general have resulted in numerous transgenic mouse models. MSH2-deficient mice, developed as a model of HNPCC, develop sebaceous tumours with MSI, mimicking the MTS. MSH6-deficient mice also are reported to develop skin tumours, although sebaceous differentiation was not specifically reported. The mechanisms by which the genomic instability accompanying loss of mismatch repair proteins promotes sebaceous tumorigenesis are not understood.

Other mouse models that develop sebaceous tumours have provided additional and serendipitous insights into the molecular pathogenesis of sebaceous tumours. Wnt and β-catenin signalling are integral for the proper differentiation of various tissues, and alterations of these signalling pathways have been linked to a variety of skin and non-cutaneous tumours. Cellular β-catenin levels are tightly regulated, existing in both cytosolic and nuclear compartments. Activation of Wnt signalling causes translocation of β-catenin to the nucleus, where it binds to proteins such as lymphocyte enhancing factor 1 (Lef-1) to permit gene transcription (Figure 10). Activating β-catenin mutations are seen in hair follicle tumours such as pilomatrixomas, along with up-regulation of sonic hedgehog signalling. Conversely, a transgenic mouse expressing a defective β-catenin binding site in the Lef-1 protein (with resulting inability to activate transcription) spontaneously developed sebaceous skin tumours. These Lef-1 transgenic mice show up-regulation of Indian hedgehog protein expression (rather than sonic hedgehog), which promotes proliferation of sebaceous precursor cells. Further work by this group has provided a model whereby levels of β-catenin drive lineage specification during development. The subsequent correlate is that aberrations in β-catenin and hedgehog signalling pathways may promote various cutaneous tumour types. Notably, dual mutations in the same allele of LEF1 were found in one-third of examined human sebaceous adenomas and sebaceomas, resulting in impaired β-catenin binding and decreased transcriptional activity (Figure 10A,B). Thus, this pathway is believed to be contributory to sebaceous tumour formation, although all of the downstream effects have not been elucidated.

The FHIT gene encodes a member of the histidine triad proteins and appears to function as a tumour suppressor. Transgenic mice heterozygous for Fhit develop a spectrum of gastrointestinal malignancies and sebaceous lesions when exposed to carcinogens. Importantly, these tumours do not exhibit MSI. Fhit has been linked to apoptosis, with FHIT mutations resulting in defective programmed cell death, and, more recently, Fhit has been shown to exert a repressive function on β-catenin transcriptional activity. FHIT mutations have been documented in human periocular sebaceous carcinomas both with and without concomitant MSI, thus providing additional support for the complex role of β-catenin signalling in sebaceous tumorigenesis.

No discussion of tumorigenesis is complete without mention of p53, the original tumour suppressor and “guardian of the genome”. When activated by cell damage, p53 degradation is decreased, with resultant increased transcriptional activation of genes that function in cell cycle arrest and apoptosis programs. Mutations in the DNA binding regions of p53 are common in skin cancers, with ultraviolet irradiation inducing predictable mutations that
promote tumour formation by the inability to halt the cell cycle or induce apoptosis. Some sebaceous neoplasms, particularly carcinomas, have been shown to display increased nuclear immunoreactivity for p53, which can correlate with mutation and/or dysregulation of p53 signalling (Figure 4D). Conversely, sebaceous tumours from transgenic Lef-1 mutated mice consistently showed an absence of p53 protein by immunohistochemical staining, which correlated with down-regulation of the binding partner ARF. These findings were hypothesized to result in tumour promotion by preventing nuclear accumulation and appropriate transcriptional activation of pro-apoptotic genes by p53. Thus, p53 signalling alterations may represent an early, primary event in a subset of sebaceous malignancies (those with nuclear accumulation of p53), while being a downstream, secondary effect within other sebaceous tumours (those with inactivating LEF1 mutations).

Summary

Sebaceous lesions encompass a spectrum from benign, cosmetically bothersome hyperplasias to aggressive carcinomas. Most commonly found in the head and neck region, these lesions are united by the presence of some degree of sebaceous differentiation. The mature sebocyte shows vaculated cytoplasm and crenulated nuclear contours, although immunohistochemistry to identify intracytoplasmic lipid or to support sebaceous differentiation may be helpful in challenging cases.

Accurate identification of sebaceous lesions is important, as the diagnosis may indicate MTS. Lesions associated with MTS frequently demonstrate mutations in genes encoding DNA mismatch repair proteins, resulting in MSI. Although MTS-associated lesions may be predicted by features such as tumour type (sebaceous adenoma or sebaceoma) and site (non-head or neck location), and perhaps by morphological features such as intratumoral lymphocytes, the identification of any sebaceous neoplasm should prompt consideration for screening for MTS. Periocular sebaceous carcinoma is much less commonly associated with MTS. Immunohistochemistry to evaluate the status of mismatch repair protein expression is increasingly used on a routine basis on these tumours.

The molecular pathogenesis of sebaceous neoplasia is still being dissected. Alterations in Wnt/β-catenin, Indian hedgehog, and p53 signalling pathways have been implicated, along with mutations in numerous tumour suppressor genes such as FHIT, DNA mismatch repair genes, and P53 itself. Further research will elucidate additional pathways. Improved understanding of the normal cutaneous developmental biology is providing key insights into the biological basis for these tumours, with hope of eventually establishing new strategies for prevention and treatment.

Acknowledgments

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Abbreviations

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<tr>
<td>CK</td>
<td>cytokeratin</td>
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<td>EMA</td>
<td>epithelial membrane antigen</td>
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<td>HNPCC</td>
<td>hereditary non-polyposis colorectal carcinoma</td>
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<td>Lef-1</td>
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**MSI** microsatellite instability

**MTS** Muir–Torre syndrome

**References**


Figure 1.

**a**, Benign sebaceous lobules are bounded by a double-layered rim of small basaloid epithelial cells. **b**, Sebaceous hyperplasia reveals multiple prominent sebaceous lobules surrounding a central dell. The normal follicle and sebaceous lobules on the left illustrate that the lobules in sebaceous hyperplasia are more superficial than normal glands.
Figure 2.
a, Sebaceous adenoma with multilobular architecture and a smooth base. 
b, Higher power of a sebaceous adenoma reveals an expanded peripheral basaloid component. c, The expansion of the basaloid component can be more subtle in sebaceous adenoma and is often accompanied by an increased prominence of the basaloid cells as well as an expansion of the number of cells. d, The cellularity of sebaceous adenomas ranges from more peripheral germinative basaloid cells to more central mature sebocytes with crenulated nuclei.
Figure 3. 

a, Sebaceomas are well-circumscribed and composed primarily of basaloid cells. b, The mature sebaceous component in sebaceoma can be rather focal.
Figure 4.

a, Periocular sebaceous carcinoma involving the lower eyelid. b, Full-thickness eyelid excision revealing sebaceous carcinoma involving the cutaneous portion of the eyelid (upper right). The mucosal surface is below. c, Periocular sebaceous carcinoma with pagetoid involvement of the overlying epithelium. d, Strong, nuclear p53 expression detected by immunohistochemistry in a periocular sebaceous carcinoma. Clinical photograph courtesy of Dr Bita Esmaeli, UT-M. D. Anderson Cancer Center, Houston, TX, USA.
Figure 5.

a, Extraocular sebaceous carcinoma showing scattered pleomorphic cells. b, Sebaceous differentiation can be focal.
Figure 6. Adipophilin immunohistochemistry in a normal sebaceous gland (a), sebaceoma (b) and periocular sebaceous carcinoma (c). It is important to identify the individual outlines of the membranes that surrounded the lipid globules within the cells for specificity. The numbers of globules will vary and are often less in number in sebaceous carcinomas with limited sebaceous differentiation.
Figure 7.
The sebaceous tumour (a) from this Muir–Torre patient shows nuclear expression of MLH1 (b) with loss of MSH2 (c) on immunohistochemistry. The overlying epidermis serves as an internal positive control.
Figure 8.
The BAT26 microsatellite shows increased variability in a sebaceous tumour from a Muir–Torre patient (lower panel) compared with normal tissue from the same patient (upper panel). This DNA-based test uses polymerase chain reaction amplification of specific loci with chromatographic determination of amplicon sizes to detect alterations in the length of the tested microsatellite.
Figure 9.
a, Sebaceous adenoma with cystic features. b, Sebaceous adenoma with keratoacanthoma-like architecture. Both of these features are thought to more specifically suggest the Muir–Torre syndrome, but more study is needed.
Dual inactivating mutations in the LEF-1 transcription factor have been documented in benign sebaceous neoplasms (a) leading to an attenuation of Wnt signalling in tumour cells (b). This not only promotes sebaceous differentiation, but also inhibits p53-mediated senescence and apoptosis. Cutaneous stem cells reside in a specialized tissue “niche” and are responsible for development and regeneration of epithelial structures including the epidermis, follicle and sebaceous gland under the influence of various signalling pathways (left). Mutations and resulting dysregulation of many of these same pathways appear to be involved in the generation of various cutaneous tumours such as that illustrated for sebaceous tumours (right). SHH, sonic hedgehog; IHH, Indian hedgehog; PTCH, patched.