Sebaceous lesions and their associated syndromes: Part I

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Sebaceous neoplasms have long been a source of confusion to dermatologists and pathologists alike. Disagreements regarding nomenclature, classification, and management have been longstanding. Sebaceous lesions represent a broad spectrum of interesting entities that range from hamartomas, hyperplasias, and benign tumors to highly malignant neoplasms. This article discusses the clinical and pathologic features of sebaceous hyperplasia, nevus sebaceus of Jadassohn, sebaceous adenoma, seboacanthoma, sebaceous epithelioma, sebaceoma, mantleoma, basal cell carcinoma with sebaceous differentiation, sebomatricoma (sebomatrixoma), and sebaceous carcinoma. Controversies regarding these lesions will be explored, and any relationship with Muir—Torre syndrome will be discussed. (J Am Acad Dermatol 2009;61:549-60.)

Learning objectives: After completing this learning activity, participants should be able to discuss controversies regarding the nomenclature of sebaceous neoplasms, discuss management strategies regarding nevus sebaceus of Jadassohn, and counsel patients about which sebaceous lesions are associated with Muir—Torre syndrome.

Key words: epidermal nevus syndrome; hereditary nonpolyposis coli cancer syndrome; linear nevus sebaceous syndrome; Lynch syndrome; Muir—Torre syndrome; nevus sebaceus of Jadassohn; sebaceoma; sebaceous adenoma; sebaceous carcinoma; sebaceous epithelioma; sebaceous hyperplasia; sebomatrixoma.

Sebaceous neoplasms are rare adnexal tumors that can present a complex challenge to the clinician. Because of their rare nature and the wide spectrum of lesions, confusion exists regarding many facets of these lesions, including nomenclature, associated syndromes, and treatment.[1,2] We hope to clarify what is currently known about each of these lesions and suggest a reasonable approach to their management.

Among the commonly recognized terms used to describe sebaceous lesions are sebaceous hyperplasia (SH), nevus sebaceus of Jadassohn (NSJ), sebaceous adenoma (SA), seboacanthoma, sebaceous epithelioma, sebaceoma, mantleoma, basal cell carcinoma (BCC) with sebaceous differentiation, sebomatricoma (sebomatrixoma), and sebaceous carcinoma (SC).[3-8]

Abbreviations used:

BCC:	basal cell carcinoma
BCC-SD:	BCC with sebaceous differentiation
MTS:	Muir—Torre syndrome
NSJ:	nevus sebaceus of Jadassohn
SA:	sebaceous adenoma
SC:	sebaceous carcinoma
SH:	sebaceous hyperplasia

Sebaceous neoplasms are associated with two different syndromes: Muir—Torre syndrome (MTS) and epidermal nevus syndrome (Table I). The different types of sebaceous lesions are discussed below.

SEBACEOUS GLANDS

Key points

- **Sebaceous glands are located everywhere hair is found**
- **Sebum secretion diminishes with age**

Sebaceous glands are associated both structurally and embryologically with the hair sheath and are usually adjacent to hair follicles, apocrine ducts, and arrector pili muscles, and they often show histologic

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Funding sources: None.
Conflicts of interest: The authors, editors, and peer reviewers have no relevant conflicts of interest.

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0190-9622/$36.00

doi:10.1016/j.jaad.2009.04.058

features of these structures.[9] The glands are either unilobular or multilobular.[9] They are attached to hair follicles with ducts, through which sebum flows.[9] The glands vary considerably in size, even within the same location of the same individual.[9] Changes occur in sebaceous glands over time. Compared with younger age groups, older individuals produce less sebum, and the sebocytes migrate slower and are retained longer.[10]

Sebaceous glands are located everywhere hair is present.[9] They are especially abundant over the head and neck, which is where sebaceous lesions are most commonly found.[9] Ectopic sebaceous glands are found on the vermillion border of the lips and labia minora (Fordyce spots), prepuce and mucosa of the penis (Tyson glands), and female areola (Montgomery tubercles).[11,12] They are common and are considered normal. Ectopic glands have also been reported in the esophagus, lacrimal caruncle, cervix, palms and soles, parotid gland, oral mucosa, and orbit.[13-18] SH occurs only in association with hair follicles; therefore, none of these ectopic glands are considered SH.[19]

CAPSULE SUMMARY

- Confusion exists regarding the nomenclature and management of many sebaceous lesions.
- Sebaceous hyperplasias are benign lesions. They are associated with Muir—Torre syndrome, but have such a high prevalence in the general population that testing is not required for patients who have sebaceous hyperplasias.
- Nevus sebaceus of Jadassohn is a hamartoma that is rarely associated with malignant neoplasms.
- Sebaceous carcinomas are malignant neoplasms with a high percentage of associated metastases.

SEBACEOUS GLAND HYPERPLASIA

Key points

- **Always associated with a hair follicle**
- **Prevalence increases with age**
- **No association with solar elastosis**
- **Associated with Muir—Torre syndrome, but high prevalence in the general population makes screening unnecessary**

SH was originally described in 1874 by Unna,[20] as discussed by Kumar et al.[21] They are characterized by yellowish or skin-colored papules that are found most commonly on the face, although other nonfacial locations, including the scrotum and chest, have been described.[13,21-23] Dermatoscopy has been reported to be helpful in their identification.[24,25] Magnification typically reveals yellowish papules with overlying telangiectasias and a central crater corresponding to the gland's ostium.[24]

SH may be seen at any age, but it appears at higher frequencies after 40 to 50 years of age and increases in prevalence over time.[10,21,26-30] De Berker et al[27] found that the prevalence of SH in a group of 107 nontransplant patients with a mean age of 51 years was 1%. Kumar and Marks found that the prevalence of SH in a group of 286 hospitalized patients with a mean age of 82 years was 26%.[29] It should be noted that these lesions may be seen as early as birth, although they are considered to be a physiologic rather than a pathologic phenomenon in that time frame.[31]

Histologically, SH appears as an array of well differentiated, mature sebaceous lobules consisting of sebocytes (Fig 1).[10,19] One or two layers of peripheral basaloid, germinative cells are seen at the periphery of the lobules.[19] The lobules are greater in number and higher in the dermis than typical sebaceous glands, but are, interestingly, not much larger.[19] They are usually attached to a cystic and dilated central pore.[19] The cross-sectional area of the gland has been shown to be significantly larger than those found in normal skin.[32] Only one gland is hypertrophied, and the surrounding glands are unaffected.[3] Based on this fact, Prioleau and Santa Cruz[3] suggest that SH would be more accurately classified as a hamartoma.

Renal transplantation or chronic immunosuppression with cyclosporin A may increase the prevalence by 10- to 30-fold.[27,33-35] This may be the result of dysplastic epithelial proliferation from either immunosuppression or as a direct effect from cyclosporin.[27] A single case report associating SH with the start of highly active antiretroviral therapy for HIV has been published.[36] Short et al[36] also speculate that SH may result from immunosuppression from HIV in this case or as a direct medication effect.

Contrary to public perception, no association between solar elastosis or skin type with regard to tanning ability and the development of SH was detected in two studies performed by Kumar et al.[21,29]

Authors have reported SHs overlying neurofibromas, melanocytic nevi, verruca vulgaris, and acrochordons.[37-39] It has been suggested that the production of growth factors or other cytokines by

Table I. Neoplasms associated with epidermal nevus syndrome or Muir–Torre syndrome*

Neoplasm	Epidermal nevus syndrome	Muir–Torre syndrome
Nevus sebaceus of Jadassohn	X	
Basal cell carcinoma with sebaceous differentiation		X
Cystic sebaceous lesions		X
Keratoacanthoma		X
Sebaceoma		X
Sebaceous epithelioma		X
Sebaceous adenoma		X
Sebaceous carcinoma		X
Seboacanthoma		X
Sebomatrixoma		X
Mantleoma		

*Note that many of the above-mentioned lesions are not considered distinct entities by all researchers.

young fibrocytes underlying the SH result in lesion formation.[38-41]

The cause of SH remains an enigma. Experiments performed on mice have shown that SH was induced by the topical application of tetradecane, a strong irritant.[42] Another mouse experiment found that the topical application of carcinogens resulted in the formation of various sebaceous neoplasms.[43] How relevant these experiments are to humans is not known.

Several rare forms of SH exist, including giant, linear, diffuse, functional familial (premature),[31] and juxtaclavicular beaded lines.[44-50] The giant form of SH has been reported several times.[51-54] The lesions are typically yellow, oily, and may be up to 5 cm in diameter.[51-54] They can present as either plaques or cyst-like lesions.[51-54] Linear SH are flat, yellow- to flesh-colored, linear papules that are several centimeters in length.[47,48] Locations have varied from the head and neck to the penis.[47,48]

Functional familial SH, which has also been termed premature or diffuse SH, occurs in young adults of both sexes, and it may run in families.[31,49,50,55,56] The age of onset is typically around puberty.[31,49,50,56] The lesions are thick and diffuse plaque–like, with pores that resemble an orange peel (*peau d'orange* appearance).[49] Lesions may occur on the face, chest, and upper back.[31,49,50,56] The patient's skin is typically very oily.[49] The periorbital, perinasal, and preauricular areas are characteristically spared.[57] Morphologically, they may resemble nevus sebaceus, epidermal nevus, or milia en plaque.[31] The histologic findings are the same as for SH.[31] Some authors believe that functional familial SH is a hamartoma that may be a subset of nevus sebaceus of Jadassohn.[31]

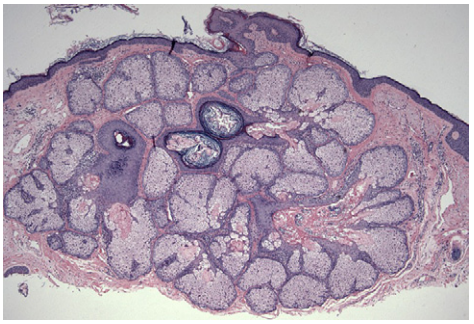

Fig 1. Sebaceous hyperplasia. Photomicrograph illustrating well differentiated, mature sebaceous lobules consisting of sebocytes. One or two layers of peripheral basaloid, germinative cells are seen at the periphery of the lobules. The lobules are greater in number and higher in the dermis than typical sebaceous glands. They are usually attached to a cystic and dilated central pore. (Courtesy of Maxwell A. Fung, MD, University of California, Davis, Sacramento, CA. Hematoxylin–eosin stain; original magnification: ×40.)

The juxtaclavicular beaded line variant was first described in 1974.[58] It appears as a linear strand of typical appearing SH papules, many with central fine hairs.[59] They are usually aligned along the relaxed skin tension lines from the shoulder to the sternum, following the line of the clavicle.[44,46,58,59] The juxtaclavicular beaded line variant occurs most frequently in the second to fifth decades of life and appears more commonly among African Americans and possibly women.[44,46,58]

Senile SH, the most common variant, is generally clinically recognizable by its yellow color, dome-shaped morphology, and ductal opening.[3] It is easily confirmed after a biopsy. It does not have malignant potential, but is associated with an increased risk of nonmelanoma skin cancer in renal transplant patients.[33]

SH may be associated with MTS.[60] MTS is characterized by the presence of a sebaceous neoplasm or keratoacanthomas and an associated internal malignancy, most often colorectal carcinoma.[60-63] However, SH is very common in the general population. Two retrospective studies of patients with biopsy-proven SH did not show any increased incidence of internal malignancies.[64,65] Therefore, given the high prevalence of SH, they are not specific for MTS.

Treatment of SH is typically for cosmetic reasons only.[66] The following therapies have been reported to be effective: photodynamic therapy, treatment with a 1450-nm diode laser, isotretinoin, bichloracetic acid, cryosurgery, electrodessication, and treatment with an argon laser, a pulsed-dye laser, and a carbon dioxide laser.[67-79]

NEVUS SEBACEUS OF JADASSOHN

Key points

- **Hamartoma with epidermal, follicular, sebaceous, and apocrine elements**
- **The risk of malignant neoplasms is small and occurs primarily in older individuals**
- **May be caused by maternal transmission of human papillomavirus to fetal ectodermal stem cells**
- **Associated with multisystem disorders as part of the linear nevus sebaceus syndrome**

NSJ is a benign lesion that occurs most frequently on the scalp (59.3%) but has also been found on the face (32.6%), preauricular area (3.8%), neck (3.2%), and locations off the head and neck (1.3%).[80] It was originally described in 1895 by Jadassohn.[81] It is a hamartoma with epidermal, follicular, sebaceous, and apocrine elements.[81] It usually presents as a verrucous, granulated, yellow-orange plaque that may be round, crescentic, or linear in shape.[82] Mehregan and Pinkus[83] suggested that there are three stages in the life of these lesions.[83] The first, or early, stage is characterized by papillomatous epithelial hyperplasia and underdeveloped hairs.[83,84] The second stage begins in puberty and is characterized by the massive development of sebaceous glands, epidermal verrucous hyperplasia, and the maturation of apocrine glands.[83,84] The last stage is characterized by the development of benign and malignant epithelial neoplasms.[83,84]

Histologically, NSJ exhibits epidermal hyperplasia that may range from slight to prominent (Fig 2).[80] Jaqueti et al,[80] in their study of 155 lesions, subclassified the epidermal hyperplasia into simple, verrucous, seborrheic keratosis–like, and acrochordon types.[80] Hair follicles may be normal in number, absent, few in number, and embryonic or normal in development.[80] Sebaceous glands, in these lesions, are similar to follicles in that they may be absent or present, immature, and normal or hyperplastic.[80] Apocrine glands are either present or absent. No other abnormality has been noted regarding their presence in NSJ.[80]

In 1979, Domingo and Helwig published their results from a slide review of 997 cases of NSJ and syringocystadenoma papilliferum.[84] They found 103 epithelial neoplasms consisting of BCCs, tricholemmomas, and unspecified other benign neoplasms.[84] Nine more aggressive malignant neoplasms were also found, including apocrine carcinoma with lymph node metastases, adnexal carcinomas with probable pilar differentiation, and squamous cell carcinoma, which later metastasized and resulted in death.[84] However, a clinicopathologic study of 155 NSJ specimens from 154 patients found no malignant lesions.[80] The authors reviewed many previous publications in which neoplasms were associated with NSJ and felt that they were all either trichoblastomas, tricholemmomas, or related to early follicular induction.[80] They suggested that early excision of NSJ to prevent malignant degeneration is unnecessary. Chun et al[85] studied 165 cases of NSJ and found only benign tumors, such as syringocystadenoma papilliferum (Fig 3) and trichoblastomas, in 5.4% of the examined specimens.[85] Cribier et al[86] examined 596 NSJ from all age groups and found five BCCs (0.8%) and 81 benign neoplasms (13.6%).[86] All of the BCCs occurred in adults.[86] Santibanez-Gallerani et al[87] studied 658 cases of NSJ excised from children 16 years of age and younger.[87] They found no evidence of BCC or other malignancies.[87] Kazakov et al[88] published a series of five cases of sebaceous carcinoma arising in association with NSJ.[88] All of the patients were female and were between 57 and 71 years of age.[88] Given the large number of studies suggesting that the vast majority of these lesions do not have associated malignancies, and those that do are seen in older age groups, observation is an alternative to early excision.

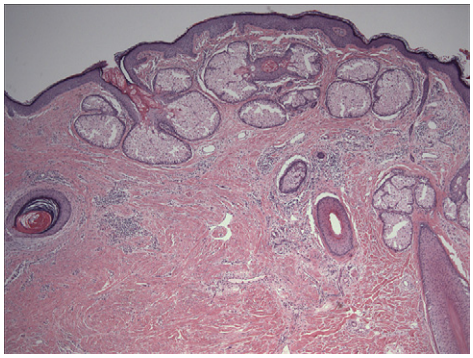

Fig 2. Nevus sebaceus of Jadassohn. Photomicrograph illustrating the presence of prominent sebaceous glands and loss of terminal hair follicles, features that are often seen in these lesions. (Courtesy of Maxwell A. Fung, MD, University of California, Davis, Sacramento, CA. Hematoxylin–eosin stain; original magnification: ×10.)

In addition to the association of NSJ with the aforementioned tumors, a syndrome involving linear sebaceous nevi with a broad spectrum of multisystem disorders has been described.[89-91] This syndrome, known as linear sebaceous nevus syndrome, will be described at greater length later in part 2 of this section of the *JAAD*.

NSJ is theorized to result from genomic mosaicism in stem cells that expand in the distribution of the lines of Blaschko.[92] A recently published study by Carlson et al[92] looked at the incidence of human

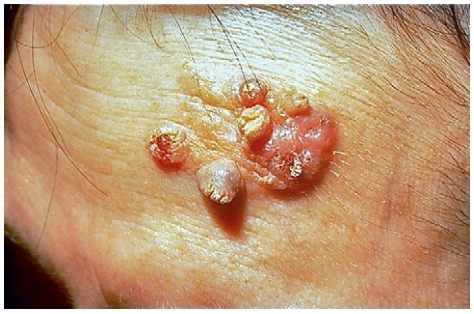

Fig 3. Syringocystadenoma papilliferum arising in a nevus sebaceus of Jadassohn. Trichblastomas and syringocystadenoma papilliferum make up the majority of tumors associated with nevus sebaceus of Jadassohn. (Courtesy of Thomas King, MD, University of California, Davis, Sacramento, CA.)

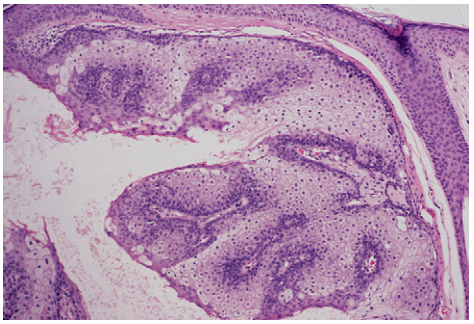

Fig 4. Sebaceous adenoma. Photomicrograph illustrating a multibolular tumor with sebaceous differentiation. Cells mature from small germinative peripheral cells at the margin of the tumor to mature sebocytes with increasing amounts of lipid in their cytoplasm. Mature sebocytes outnumber small germinative cells, a differentiating feature from sebaceomas. (Courtesy of Maxwell A. Fung, MD, University of California, Davis, Sacramento, CA. Hematoxylin–eosin stain; original magnification: ×100.)

papillomavirus infection (HPV) in 44 NSJs and found HPV to be present in 82% of their specimens.[92] Histologically, the tissue showed evidence of HPV-associated changes.[92] In situ hybridization revealed viral integration of HPV DNA into genomic DNA in 18 of 28 tested samples.[92] The results suggest that maternal transmission of HPV DNA to fetal ectodermal stem cells could result in epigenomic mosaicism and altered skin development.[92]

In terms of an alternative treatment to excision, photodynamic therapy, carbon dioxide laser resurfacing, and dermabrasion have been advocated.[93-95] None of these treatment modalities completely removes the lesion, and there is therefore a risk of recurrence or the potential for the development of tumors in the residual lesion.

SEBACEOUS ADENOMAS

Key points

- **Benign neoplasm of sebaceous origin**
- **Germinative cells are present beyond the normal one to two layers seen in sebaceous hyperplasia, but still make up proportionally less of the lesion than mature sebocytes**
- **Associated with Muir–Torre syndrome**

SAs are benign, multilobular tumors with sebaceous differentiation (Fig 4).[3,4,66] The lobules may vary in size and shape, and extend into the mid to reticular dermis.[3] They are typically separated by septa of connective tissue or strands of epithelial cells.[3] The tumors may be polypoid or slightly elevated.[3] Surface epithelium either adjoins or is replaced by the tumor.[3]

SAs are similar to SH in that they progress from small germinative peripheral cells at the margin of the lobules to mature sebocytes with increasing amounts of lipid in their cytoplasm.[3] The differentiating feature of these lesions from SH is the expansion of basaloid cells beyond the normal one to two layers, as compared to SH.[19] Mature sebocytes still outnumber germinative cells, which is a key factor in distinguishing these lesions from BCC with sebaceous differentiation or sebaceoma.[3] The central sebocytes often reveal holocrine secretion and are larger in size with an eosinophilic, vacuolated cytoplasm.[19] A sebaceous gland–like lobular architecture is maintained, but the lesion is larger than normal.[19] Nuclei in the immature and differentiated sebocytes are indented by lipids in the cytoplasm.[4,19]

These tumors are rare and may be solitary or multiple in number.[96] The lesions are characterized by smooth, well circumscribed, speckled yellow papules usually <0.5 cm in diameter, although lesions >9 cm have been documented.[4,96] Rulon and Helwig[4] reported a series of 46 SAs; 70% of their cases were found on the head and 30% on the neck, trunk, and legs.[4] The average age of those affected was 60 years.[4] Locations on the oral mucosa have also been reported.[97,98] Symptoms reported by Rulon and Helwig[4] included bleeding (50%), ulceration (10%), and pain (30%). Three of 28 patients studied by Rulon and Helwig[4] with a follow-up of at least 6 months in length had a recurrence of their tumors following excision. SAs are the most common sebaceous neoplasm associated with MTS, appearing in at least 68% of patients.[66,99] The lesions occur on the trunk more often than the head and neck in MTS compared to sporadic cases.[100]

Excision appears to be an adequate treatment for these lesions. There have been no reports of metastases resulting from these tumors.

SEBOACANTHOMA

Key points

- **Tumors have the architecture of keratoacanthomas but are composed of sebaceous lobules**
- **Associated with Muir–Torre syndrome**

A subtype of SA, termed seboacanthoma by Pinkus,[101] contains elements of both keratoacanthoma and SA.[60] Histologically, Pinkus[101] described a tumor that simultaneously expressed two different pathways of maturation. He noted the presence of large cells that produce lipid and keratin.[101] The tumors have the architecture of a keratoacanthoma, but contain well differentiated sebaceous lobules.[102,103] Clinically, these lesions are noted by Naylor[7] to present as 1- to 4-mm verrucoid, sessile papules, 1 to 2 mm in height, located on the face.[7] They are very rare, and case reports have described them primarily in patients with MTS, suggesting an association.[60,102]

SEBACEOMA (SEBACEOUS EPITHELIOMA)

Key points

- **Controversy exists regarding the nomenclature of this benign tumor**
- **Associated with Muir–Torre syndrome**

The term sebaceous epithelioma has been used to describe multiple types of benign sebaceous proliferations with less differentiated sebocytes.[1] This terminology is a source of confusion.[1] In the past, pathologists have used the term carcinoma for lesions that are locally infiltrative but rarely metastasize.[1] Dermatologists, alternatively, have used the term epithelioma to describe these types of lesions.[1] Therefore, "sebaceous epithelioma" and "sebaceous carcinoma" have been used both as synonyms and to describe two completely different lesions with different prognostic outcomes.[1,104] Sebaceous epithelioma has also been used synonymously with BCC with sebaceous differentiation by some authors.[3]

Troy and Ackerman[1] suggested completely abandoning the term sebaceous epithelioma. They proposed the term "sebaceoma" instead, to mean a benign adnexal neoplasm of sebaceous origin, consisting of basaloid cells often with duct- or cyst-like structures situated in the papillary dermis surrounded by sclerotic stroma (Fig 5).[1] Whether called sebaceous epithelioma or sebaceoma, these lesions are benign, and treatment is driven by cosmetic or functional considerations. Like SAs, these neoplasms can be associated with MTS.[60]

Clinically, the lesions are described as yellowish papules with rolled borders (Fig 6).[3] They are typically solitary and measure <1 cm in diameter, but larger lesions have been reported.[105] Ulceration and bleeding are common findings.[3] As with SAs, excision is considered adequate treatment for these lesions.

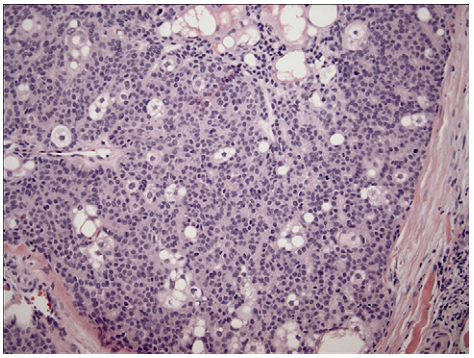

Fig 5. Sebaceoma. Photomicrograph illustrating a benign neoplasm consisting of basaloid cells with sebaceous differentiation. The neoplasm is surrounded by a sclerotic stroma. Germinative cells outnumber sebocytes, a feature differentiating this tumor from sebaceous adenoma. (Courtesy of Maxwell A. Fung, MD, University of California, Davis, Sacramento, CA. Hematoxylin–eosin stain; original magnification: ×200.)

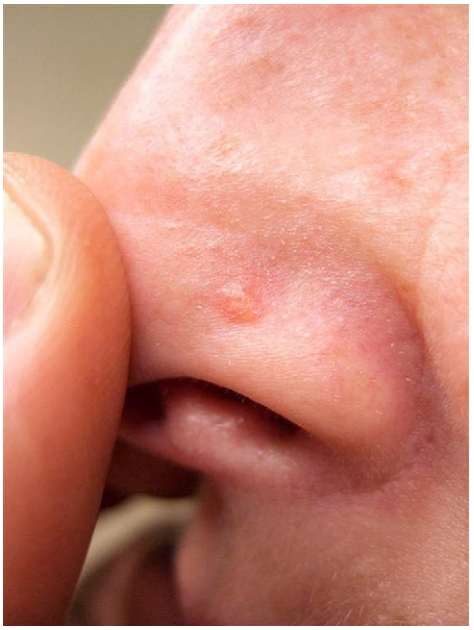

Fig 6. A sebaceoma on the left nasal ala. These usually manifest as yellow papules with rolled borders. (Courtesy of Jeffrey Newman, MD, PhD, Puyallup, WA.)

BASAL CELL CARCINOMA WITH SEBACEOUS DIFFERENTIATION

Key points

- **This lesion is controversial, with many believing it is inseparable from sebaceoma**
- **If this is a separate lesion, its incidence is rare. It is associated with Muir–Torre syndrome**

BCC with sebaceous differentiation (BCC-SD) is a controversial term. Some authors consider it identical

to sebaceous epithelioma.[3,4] Those that believe this to be a distinguishable lesion from sebaceous epithelioma have suggested the following criteria to define BCC-SD: (1) aggregations of follicular germinative cells with silhouette of malignancy, (2) cells at the periphery of aggregations that are columnar and arranged in a palisade, and (3) clefts between aggregations of neoplastic germinative cells and adjacent stroma.[8] Misago et al[8] suggest that this is different from a sebaceoma in that the architecture of sebaceomas is benign and that of BCC-SD is malignant. Also, the peripheral cells of sebaceomas are not arranged in palisades and do not possess clefts between tumor lobules and surrounding stroma as BCC-SD does.[8] The degree of sebaceous differentiation seen in BCC-SD is also stated to be much lower than that seen in sebaceoma and sebaceous carcinoma.[8] No guide is offered as to what percent of the lesion should have sebaceous differentiation as a way to distinguish this entity.[8] If this lesion exists as a separate entity, its incidence appears to be rare.[8,65,106] Regardless of how these lesions are defined, they have been associated with MTS, and MTS should be considered when the diagnosis of BCC-SD is made.[60]

SEBOMATRICOMA (SEBOMATRIXOMA)

Key points

- **Some authors propose one unifying term for all benign neoplasms with sebaceous differentiation**

The clinical relevance of differentiating benign neoplasms of sebaceous origin is still being debated. Sáchez Yus et al[107] reviewed 19 benign sebaceous neoplasms and suggested that SA and sebaceoma represent polar ends of a spectrum of benign neoplasms with sebaceous differentiation. They suggested the term sebomatrixoma to represent this set of neoplasms.[107] Further confusing the matter of nomenclature, Misago and Narisawa[108] state that it is sometimes difficult to distinguish sebaceous carcinoma from sebaceous adenoma or sebaceous epithelioma. Others use the term SA to describe all these benign lesions.[109] The terminology for these lesions remains controversial.

MANTLEOMA

Key points

- **The mantle is a structure of the sebaceous gland cycle**
- **Some suggest that fibrofolliculomas are hamartomas with differentiation towards the sebaceous mantle, though this is not universally agreed upon**

The mantleoma is an uncommon sebaceous hamartoma.[106] The mantle is a structure of the sebaceous gland cycle.[106] Much like hair follicles, sebaceous glands are theorized to have cycles.[106] In the resting phase of the cycle, the mantle consists of cords of undifferentiated cells that originate from the infundibulum of a hair follicle and descend beside the follicle in the form of a mantle or skirt.[106] Sebocytes appear at the end of these cords and eventually develop into sebaceous glands.[106] It is hypothesized that sebaceous glands then eventually involute, becoming undifferentiated mantles, which completes the cycle.[106] Mantleomas are most often found on the face.[106] Histologically, mantleomas vary in complexity.[106] Early neoplasms consist only of cords of undifferentiated epithelial cells that radiate from the follicular infundibulum.[106] Later on, these cords interweave in a retiform pattern that contains sebocytes of varying degrees of vacuolization and sebaceous ductal structures.[106]

Some suggest that fibrofolliculomas are hamartomas with differentiation towards the mantle, although this is not universally agreed upon.[110] Regardless, these lesions are benign, and atypical neoplastic cells are not seen.[106] Clinically, mantleomas appear as either solitary or multiple, dome-shaped, yellow or white papules that are 2 to 4 mm in size.[111]

SEBACEOUS CARCINOMA

Key points

- **Malignant neoplasm is most often found in the periocular area**
- **Its nonspecific appearance often leads to a misdiagnosis**
- **Preliminary evidence exists showing the better efficacy of Mohs surgery over wide excision**
- **Associated with Muir–Torre syndrome**

SC is a rare malignant neoplasm.[112] About 75% of sebaceous neoplasms are periocular in location.[113] These tumors develop from sebaceous glands and can be found in any location where these glands are present.[114,115]

The most frequent clinical presentation is a painless subcutaneous nodule.[116] Other presentations include diffuse thickening of the skin, pedunculated lesions, or as an irregular mass (Fig 7).[116] The protean appearance of SCs complicates diagnosis. It often presents with an appearance similar to more common benign lesions and is frequently misdiagnosed.[115,117-119] It is not unusual for a SC to be treated multiple times as a chalazion before the diagnosis is made.[117] An incomplete biopsy specimen, either because of its proximity to the eye or because the diagnosis is not in the clinical

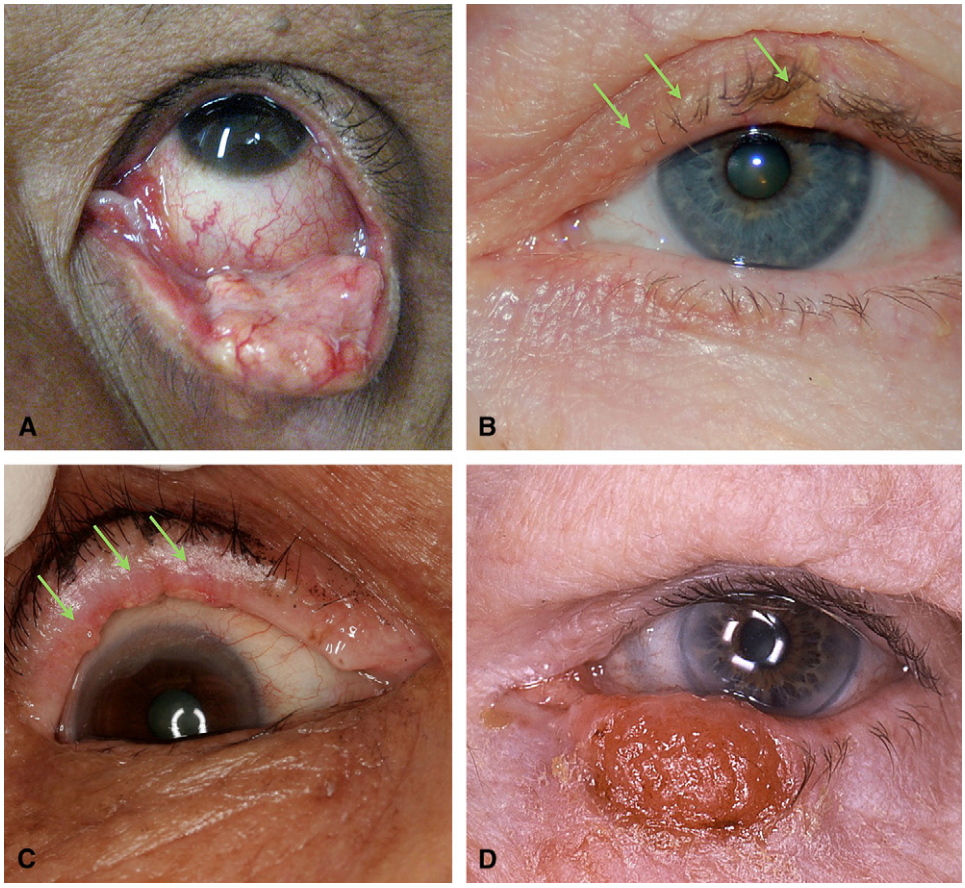

Fig 7. Sebaceous carcinomas may take many different forms. Parts (**A**) and (**D**) show obvious tumors. Parts (**B**) and (**C**) illustrate why these lesions can be difficult to diagnose. The *arrows* indicate a subtle yellow plaque along the eyelid margin (**B**) and an inflamed thickened eyelid margin (**C**). (**A** and **B**, Courtesy of Lily Koo Lin, MD, University of California, Davis, Sacramento, CA. **C** and **D**, Courtesy of David Zloty, MD, University of British Columbia, Vancouver, BC, Canada.)

differential at the time, can both complicate matters and delay therapy.[117]

Histologically, SCs may be classified as well, moderately, or poorly differentiated.[120] In addition, four patterns are recognized by most authorities: lobular, comedocarcinoma, papillary, and mixed.[115] Typical lesions have an irregular lobular pattern with sebaceous and undifferentiated cells.[116] The tumor cells show a marked variation of nuclear shape and size, hyperchromatism, basaloid appearance, and high mitotic activity.[116] The undifferentiated cells have eosinophilic cytoplasm with lipid granules that give them a frothy appearance.[116] Atypical keratinizing cells may be present.[116] The spread of tumor cells into the adjacent epithelium (pagetoid spread) is also a known feature (Fig 8).[116] The oil red O stain, Sudan IV stains, epithelial membrane antigen, and Leu-M1 immunostains may be helpful in discriminating sebaceous carcinomas from other tumors.[116,121,122]

SCs have high rates of recurrence and metastasis.[120,123-130] Mortality rates range from 9% to 50%.[120,128,131-133] With earlier recognition, however, these rates appear to be declining.[128,134-136] Ocular SC has recurrence rates ranging from 11% to 30% with distant metastasis occurring in 3% to 25%.[136,137] It was initially thought that extraocular SC was much less aggressive, but a study with 91 cases of extraocular (head or neck) SC showed a recurrence rate of 29%, with 21% developing metastases.[138]

Five- to 6-mm excision margins are often referred to as standard, but have been associated with a 5-year mortality rate of 18% and recurrence rates of up to 36% at 5 years.[115,134] A recent study showed recurrence rates of 30% after standard excision and 11% after Mohs micrographic surgery.[139] Although SC is thought to be resistant to radiation therapy, some case reports have shown remission with treatment.[140] Exenteration is advocated in situations where the orbit or significant portions of the bulbar

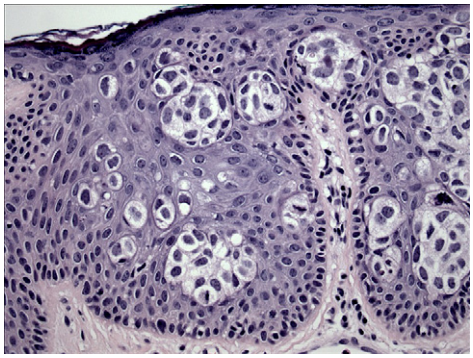

Fig 8. Sebaceous carcinoma. Photomicrograph illustrates prominent upward migration of neoplastic cells of sebaceous origin (pagetoid spread). Nuclear pleomorphism, prominent nucleoli, and mitotic figures can be seen. (Courtesy of Maxwell A. Fung, MD, University of California, Davis, Sacramento, CA. Hematoxylin–eosin stain; original magnification: ×400.)

conjunctiva are involved.[115] These tumors are also associated with MTS.[60]

CYSTIC SEBACEOUS LESIONS

Key points

- **In the past, these lesions were highly associated with Muir–Torre syndrome**
- **A recent study throws some doubt about their universal association with Muir–Torre syndrome**

Cystic variants of sebaceous lesions that range from hyperplasia to adenoma, and possibly carcinoma, have been identified.[141-144] In the past, all of these lesions were associated clinically or by genetic evaluation with MTS.[108,141-145] However, a recent study found no statistically significant correlation between cystic change and DNA mismatch repair deficiency, which is a marker for MTS.[100] It was not known if any of the patients studied had MTS.[100]

CONCLUSION

Sebaceous neoplasms represent a broad spectrum of lesions, which range from benign to highly malignant. NSJ is only rarely associated with the development of malignant neoplasms, and therefore observation may be a reasonable alternative to early excision. Alternatively, SCs are tumors that are very aggressive and sometimes highly difficult to detect. They should be considered in the differential diagnosis of any eyelid lesion. Confusion regarding the nomenclature, diagnosis, and management of these lesions remains considerable. This article provides a guideline for understanding and managing this class of lesions.

We would like to thank Maxwell A. Fung, Heidi Goodarzi, Keira Barr, Melissa Reyes, and Victoria Sharon for their work in editing the manuscript. We thank Maxwell A. Fung for providing the histologic images for the SA, sebaceoma, SH, and nevus sebaceus of Jadassohn, and Thomas King who provided the image of the syringocystadenoma arising in a nevus sebaceus of Jadassohn.

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