The Germinative Preponderance-Sebaceous Epithelioma

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Abstract

Sebaceous epithelioma is a benign, exceptional, distinctive neoplasm comprised of basaloid cells and mature sebocytes. Although a sporadic neoplasm, Muir-Torre syndrome can be frequently associated with sebaceous epithelioma. Benign sebaceous epithelioma, additionally termed as sebaceoma is indicative of sebaceous neoplasm exceeding >50% basaloid cell component and demonstrates yellow papules, nodules or plaques predominating on sites of enhanced sebaceous glands. Dermoscopy delineates yellow-tinged, granular articulations with fine, curvilinear capillaries and vascular formations. Sebaceoma incorporates an admixture of undifferentiated basaloid cells and differentiated sebaceous cells. Basaloid cells enunciate a cytoplasmic vacuolation and sebaceous cells are clear and lipid rich. Histological variants of sebaceoma include carcinoma-like, sinusoidal, reticulated, cribriform, rippled and sebaceoma with Verocay body-like features. Immune reactivity to adipophilin, epithelial membrane antigen (EMA), cytokeratin 5(CK5), cytokeratin 6(CK6) and p40 are elucidated. Sebaceoma requires a distinction from basal cell carcinoma with sebaceous differentiation and trichoblastoma with sebaceous differentiation. Surgical resection of the neoplasm with a narrow surgical resection margin is the preferred therapeutic option.

Preface

Sebaceous epithelioma is described as a benign, exceptional, distinctive neoplasm of adnexal epithelium depicting sebaceous differentiation and can be additionally designated as sebaceaoma. Sebaceous epithelioma is a benign sebaceous neoplasm comprised of basaloid cells and mature sebocytes. Muir-Torre syndrome can be frequently associated with sebaceous epithelioma, although it appears as an isolated or sporadic neoplasm. Sebaceous epithelioma can be misinterpreted as a terminology for low grade sebaceous carcinoma, basal cell carcinoma with sebaceous differentiation or sebaceous proliferations of indeterminate malignant potential [1,2].

Disease Characteristics

The face and eyelids display innumerable, modified sebaceous glands configuring as Zeis glands and Meibomian glands. Sebaceous tumors exemplifying as sebaceous adenoma, sebaceous epithelioma and sebaceous carcinoma generally are cutaneous indicators of an internal, visceral malignancy as encountered with the Muir-Torre syndrome. Sebaceoma is adopted as a nomenclature for sebaceous neoplasm exceeding >50% basaloid cells whereas sebaceous adenoma denominates beneath <50% basaloid cells. Sebaceoma of the eyelid appears with an incidence of 4.7% to 14.28% in the general population. Sebaceoma depicts a female predominance with an estimated female to male proportion of 4:1. Majority of the implicated individuals are within the sixth to ninth decade, although the tumefaction can appear at any age [3,4]. Sebaceoma preponderantly occurs on the head and neck, face and scalp and delineation of the aforesaid neoplasm within sites beyond the head and neck can indicate a concurrence with Muir-Torre syndrome. Thus, extensive evaluation is required to exclude concomitant systemic disease and neoplasia. However, sebaceoma can be sporadic and solitary and lack a concordance with an internal, visceral malignancy or Muir-Torre syndrome. The lesion is devoid of concurrent regional lymph node enlargement [3,4].

Clinical Elucidation

The essentially benign sebaceous epithelioma, additionally termed as sebaceoma, demonstrates yellow papules, nodules or plaques which are predominant in areas of enhanced quantification of sebaceous glands. Painless, firm, non-tender nodules with well circumscribed
borders and a varying dimension can appear on the eyelids or
adjunctive locations. Yellow to orange or flesh colored papules,
nodules or tumefaction can be typically elucidated in sebaceoma.
Yellowish white occipital nodules with a smooth extraneous surface
and magnitude in millimeters can also be enunciated. A thorough
clinical investigation is necessitated in order to exclude a Muir-
Torre syndrome or emergence of a concomitant internal, visceral
malignancy. Dermoscopic evaluation demonstrates yellow-tinged,
granular articulations with accompanying finely delineated,
curvilinear capillaries and vascular arrangements—a feature
recapitulated in sebaceous carcinoma [3,5].

**Histological Elucidation**

Sebaceoma typically represents as a solitary, well circumscribed,
frequently yellow nodule or a poorly delineated plaque. Gross
examination delineates grainy, yellowish, oily material accumulated
within segregated locules. Morphological enunciation of the
adnexal neoplasm incorporates an admixture of undifferentiated
basaloid cells and differentiated sebaceous cells. The tumefaction
is predominantly comprised of basaloid cells and loci of sebaceous
differentiation with mature sebaceous cells. Basaloid cells can
enunciate a cytoplasmic vacuolation and sebaceous cells are clear
and lipid-rich [4,5]. Superimposed stratified squamous epithelium
can depict mild induration and a prominence of vasculature. Mitotic
activity is inconspicuous, and the neoplasm is devoid of stromal
invasion. Dermal nodules comprised of a cellular component
with irregular outline are enunciated with varying degrees of
incrimination of superimposed stratified squamous epithelium.
As the tumefaction is constituted of undifferentiated basaloid cells
and mature, differentiated sebocytes, the neoplasm is configured
by a greater (>50%) proportion of basaloid cells. Morphological
exemplification of a mammoth, intradermal tumor with cord-like
structures and tumor cell nests of undifferentiated basaloid cells
can also be demonstrated. The cellular aggregates appear parallel
along the intervening interstitial septa in order to configure a
predominantly trabecular pattern [5,6]. Emergence of miniature
keratocysts within the papillary dermis or upper reticular dermis
can be delineated. Minimal quantities of lipid-laden, vacuolated
cells are exhibited within the tumor cell aggregates. Mitosis is
infrequent and appears with the ratio of beneath <1 mitotic
figure per 10 high power fields. Basaloid or germinative cells are
accompanied with cells of sebaceous differentiation. However,
germinative cells usually outnumber mature sebocytes, a feature
which distinguishes sebaceoma from sebaceous adenoma. The
neoplasm is generally surrounded by a sclerotic, fibrous tissue
stroma. Histological variants of sebaceoma are enumerable such as
carcinoid-like, sinuosoidal, reticulated, cribriform, rippled and
sebaceomas with Verocay body-like features [3,4]. Rippled variant
of sebaceoma can exhibit a monomorphic articulation of miniature,
cigar shaped, basaloid cells arranged in a parallel, linear pattern
with an absence of septa betwixt rows of basaloid cells. Sinuosoidal
and carcinoid-like tumor evolution within a sebaceous neoplasm
can be misinterpreted as a malignant transformation. Admixture of
trabecular pattern and ribbon-like arrangements can be delineated.
Trabecular arrangements can be enunciated singularly and entirely
with a specific lesion. Variants of sebaceoma with keratoacanthoma-
like features or preponderant cystic modifications usually indicate
the concurrence of a Muir-Torre syndrome. Sebaceomas with tumor
architecture akin to carcinoid-like pattern can be particularly
elicited in malignant sebaceous carcinoma [5,6].

**Immune Histochemical Elucidation**

A proliferative activity beneath <10% on immune staining with
diamino-benizidine with an intense, peripheral immune
reactivity is exemplified. Proliferative activity of the tumefaction
can also be assessed with Ki-67 (MIB-1) index which appears
below < 10%. Regular sebaceous glands are reactive to p21WF1
immune antibodies, particularly within the differentiating fraction
of sebaceous glands. Aforementioned compartment depicts a distinct
configuration from the peripheral cellular cycle composed of Ki-
67 reactive basaloid cells. Proliferative index as evaluated with
MIB-1 can appear at an estimated 2% [3,4]. Sebaceoma cogitates
an identical distribution of immune markers as that of normal
sebaceous glands although the proliferative, cellular segment is
expanded. Immune reactivity to adipophilin and epithelial
membrane antigen (EMA) is delineated in zones of lipid-rich,
vacuolated tumor cells. Immune reactivity to cytokeratin 5 (CK5)
and cytokeratin 6 (CK6) along with p40 are elucidated in cord-like
nests and vacuolated tumor cells. Immune reactive p40 can be
elucinated in sebaceous carcinoma along with basal or
generative layer of sebaceous epithelium. Sebaceous cells non-
reactive to adipophilin although immune reactive to p40 can
represent an immature basaloid or generative layer of sebaceous
epithelium, in concordance with a typical, benign sebaceoma [7,8].

**Genetic Elucidation**

Muir-Torre syndrome is contemplated as phenotypic variant
of hereditary non-polyposis colorectal carcinoma syndrome
(HNPCC) or Lynch syndrome. Aforementioned genomic manifestation
is engendered by germline mutations occurring within one allele of
DNA mismatch repair genes cogitated with MLH1, MSH2, MSH6
and PMS2. Muir-Torre syndrome is frequently accompanied with
sebaceous neoplasia, chiefly sebaceous adenoma along with
colorectal malignancies, genito-urinary and adjunctive visceral
adenocarcinoma. Chromosomal mutations of MSH2 gene are
frequently delineated in Muir-Torre syndrome [7,8].

Suspected emergence of Muir-Torre, as indicated by a personal
or family history, discernment of genito-urinary or breast
malignancies or an elderly subject with numerous sebaceous
neoplasm distant from locations within the head and neck, can be
benefited with extensive immune- histochemical evaluation of
mismatch repair genes or assessment of microsatellite instability.
Deficient enunciation of MLH1 on account of germline mutations
or a somatic hyper-methylation cannot be discerned on cogent immune reactions and a few germline, missense mutations can be misinterpreted as normal immune reactivity as antigenically complete, nonfunctional proteins can be generated [8,9]. Microsatellite instability (MSI) assay as performed on formalin fixed tissue is sensitive and appropriate for ascertaining individuals with germline mismatch repair (MMR) genetic derangements, rather than employing immune-histochemistry. Prognostic outcomes are determined as MSI-H with enhanced proportion of microsatellite instability and MSI-L delineating minimal quantities of microsatellite instability (Figure 1-12).

**Figure 1:** Sebaceoma with lobules of sebocytes and abundant, peripheral basaloid cells [11].

**Figure 2:** Sebaceoma with lobulated, lipid-rich sebaceous cells and a perimeter of undifferentiated basaloid cells [12].

**Figure 3:** Sebaceoma with numerous aggregates of basaloid cells and interspersed sebocytes [13].

**Figure 4:** Sebaceoma with nests and clusters of undifferentiated basaloid cells and tiny aggregates of sebaceous cells [13].

**Figure 5:** Sebaceoma with several, enlarged sebaceous cell clusters with a border of basaloid cells and a superimposed stratified squamous epithelium [14].

**Figure 6:** Sebaceoma with a dermal exponent of basaloid cell aggregates, dispersed sebaceous cells and superficial squamous epithelium [15].

**Figure 7:** Sebaceoma with lobulated, dermal aggregates of undifferentiated basaloid cells and intermingles sebocytes [15].
Evaluation of germline mutations can be adapted as blood leukocyte genomic sequencing, a modality which is optimal in the recognition of germline mutations within the MLH1, MSH2, MSH6 and PMS2 genes. Instances devoid of germline mutations can occur, although the neoplasm can depict accompanying mismatch repair deficiencies along with involvement of associated mismatch repair proteins. Somatic mutations or hyper-methylation of the promotor regions can concur. Sebaceomas can occur as sporadic neoplasm with an absence of concurrent Muir-Torre syndrome [8,9]. Specific genomic features can quantify the prognosis of sebaceoma. Absence of nuclear staining for MLH1, MSH2, MSH6 or PMS2 is indicative of microsatellite instability and favours the ascertainment of Muir-Torre syndrome. Genomic mutations of MLH1 and MSH2 genes are cogent in engendering numerous instances of phenotypic microsatellite instability. Deficiency of MSH2 and MSH6 is concomitant on account of the configuration of a heterodimer mismatch repair (MMR) recognition factor generated with specific protein products of MSH2 and MSH6. MSH6 is genetically unstable in the absence of MSH2 and is rapidly deteriorated [7,9].

Differential Diagnosis

Sebaceoma requires a distinction from basal cell carcinoma with sebaceous differentiation. Basal cell carcinoma depicts a predominant peripheral palisading, configuration of clefts surrounding the tumor lobules and incidental sebaceous differentiation. Basal cell carcinoma is immune reactive for BerEP4 whereas a sebaceoma is non-reactive. Sebaceous adenoma is composed of basloid cells expressed beneath <50%, in contrast to a sebaceoma which demonstrates above >50% of basloid, germinative cells [4,5]. Sebaceous carcinoma displays analogous features of malignancy such as nuclear pleomorphism, nucleolar prominence, an infiltrative pattern of tumor evolution and an enhanced mitotic activity, in contrast to a sebaceoma. Trichoblastoma with sebaceous differentiation can also be misinterpreted as a sebaceoma and requires distinction. However, trichoblastoma delineates distinct foci of hair differentiation and papillary mesenchymal bodies [4,5].

Therapeutic Options

Surgical excision of the neoplasm is the preferential therapy. Surgical resection of the nodule with a narrow surgical margin is
optimally recommended. Reconstructive surgery of the implicated site can be adopted for a superior cosmetic result and to reduce the probability of malignant transformation. Thus, on account of possible malignant transformation within a sebaceous epithelioma and potential, localized reoccurrence, surgical extermination of the tumor with reconstructive surgery is a preferred therapeutic option [9,10]. Upon efficacious diagnosis, further treatment is expendable. However, a comprehensive surgical excision is optimally performed in instances of a partial biopsy or suspicion of a basal cell carcinoma with sebaceous differentiation or sebaceous carcinoma [11-20].

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