Title: Update on the Pathology, Genetics and Somatic Landscape of Sebaceous Tumours

Short running title: Sebaceous tumours

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Abstract

Cutaneous sebaceous neoplasms show a predilection for the head and neck area of adults and include tumours with benign behaviour, sebaceous adenoma and sebaceoma, and sebaceous carcinoma with potential for an aggressive disease course at the malignant end of the spectrum. The majority of tumours are solitary and sporadic, but a subset of tumours may be associated with Lynch syndrome, also known as hereditary non-polyposis colon cancer (HNPCC) and previously referred to as Muir-Torre syndrome (now known to be part of Lynch syndrome). This review provides an overview of the clinical and histological features of cutaneous sebaceous neoplasia with an emphasis on differentiating features and differential diagnosis. It also offers insights into the recently described molecular pathways involved in the development of sebaceous tumours and their association with Lynch syndrome.

Keywords:

Sebaceous neoplasms; sebaceous adenoma; sebaceoma; sebaceous carcinoma; Muir-Torre syndrome; Lynch syndrome

Introduction

The spectrum of cutaneous sebaceous neoplasms ranges from benign sebaceous adenoma and sebaceoma to sebaceous carcinoma with potential for aggressive behaviour [1]. The majority of tumours are solitary and sporadic with a predilection for the head and neck area of elderly adults. Multiple sebaceous neoplasms and tumours presenting outside the head and neck may be seen in patients with Lynch syndrome or hereditary non-polyposis colorectal carcinoma, which has also been referred to as Muir-Torre syndrome (MTS) [2, 3].

The diagnosis of sebaceous tumours is often challenging and relies entirely on histological examination. The reliable separation of sebaceoma from its malignant counterpart sebaceous carcinoma remains particularly problematic, especially on partial samples [1]. Over the past few years our understanding of the molecular pathways and genetic events involved in the pathogenesis of sebaceous tumours, especially sebaceous carcinomas, has evolved significantly [4, 5].

This manuscript reviews our current understanding of sebaceous neoplasia. It discusses the clinico-pathological features of sebaceous adenoma, sebaceoma and sebaceous carcinoma with an emphasis on differential diagnosis followed by an overview of sebaceous tumours associated with Lynch syndrome / HNPCC and a review of the molecular pathological and genetic changes associated with these tumours.

Sebaceous adenoma

Clinical features: Sebaceous adenoma is rare and presents as solitary, skin coloured to yellow papules or nodules, which occasionally ulcerate. They are located in the head and neck area

with a predilection for the nose and cheek of middle-aged to elderly adults. Rarely, these tumours are multiple and involve other anatomical sites [6].

Histological features: Sebaceous adenomas are well-circumscribed and lobulated neoplasms within upper to mid dermis and a connection with the overlying epidermis (Fig.1a). Centrally, they are composed of mature sebaceous cells containing abundant pale staining, vacuolated cytoplasm with centrally located, indented or scalloped nuclei (Fig.1b). The periphery of the tumour lobules is composed of immature germinative cells with scant to moderate amounts of basaloid cytoplasm and round to oval vesicular nuclei (Fig.1c). The outer germinative layer is typically more than two cell layers thick and shows increased mitotic activity. By definition, the germinative cell population comprises less than 50% of all tumour cells [2]. Holocrine secretion is noted in the centre of the tumour. A keratoacanthoma-like or predominantly cystic growth pattern is rarely observed (Fig.1d). Ulceration may be present but atypical mitoses or tumour necrosis are not noted.

Immunohistochemistry: Immunohistochemistry (IHC) is not required to confirm the diagnosis.

Behaviour and Treatment: The tumours are benign, and they are treated by simple excision.

Differential diagnosis: Sebaceous hyperplasia is characterized by multiple, normal appearing sebaceous lobules draining into a common central duct, often in association with a hair follicle. In contrast to sebaceous adenoma, the layer of peripheral basaloid germinative cells is not expanded and does not exceed one to two cell layers. Ectopic sebaceous glands are found on special sites such as the areola (Montgomery tubercles), the penis (Tyson glands) and the lips (Fordyce spots). They are not associated with a central hair follicle. Sebaceoma is distinguished by a predominance of the basaloid germinative cell population of more than 50 % of all tumour cells [2, 7].

Sebaceoma

Clinical features: Sebaceomas most commonly affect the head and neck area of the elderly with a female predilection and a median age of 70 years [1, 2, 8]. The tumours can reach several centimetres in size and appear as solitary skin-coloured or yellow nodules. They are rarely multiple and may arise within a naevus sebaceous [1, 2, 8].

Histological features: Sebaceoma is a sharply demarcated uni- or multilobular neoplasm within the dermis with variable connection with the overlying epidermis (Fig.2a). The tumour is composed predominantly (>50% of tumour cells) of immature germinative cells characterized by scanty to moderate amounts of basaloid cytoplasm and central vesicular nuclei containing eosinophilic nucleoli (Fig.2b). Occasional intracytoplasmic lipid vacuoles can be appreciated. The mitotic activity may be brisk but atypical mitoses, nuclear pleomorphism or tumour necrosis are not encountered. Mature sebaceous cells are scattered throughout the tumour singly or in small clusters (Fig.2c). Sebaceous ducts and holocrine secretions are usually present within the tumours (Fig.2d and 2e). Sebaceomas may exhibit distinct growth patterns that provide helpful morphological clues to the diagnosis. These include rippled, sinusoidal or labyrinthine and carcinoid-like patterns (Fig.2f) [9-11]. The tumours may also contain infundibulocystic structures, squamous metaplasia and areas of apocrine differentiation (Fig.3a) [12]. Cystic change and a keratoacanthoma-like architecture are rarely observed (Fig.3b and c).

Immunohistochemistry: Sebaceoma expresses high molecular weight cytokeratins, p63 and p40. They are commonly positive for CK7 but negative for CK20 and BerEP4. The sebaceous

differentiation can be highlighted by epithelial membrane antigen (EMA) or adipophilin staining in the mature sebaceous cells (Fig.3d) [7, 13].

Behaviour and treatment: The tumours are benign with only rare local recurrence following simple excision [8].

Differential diagnosis: Most important is the distinction from sebaceous carcinoma in view of the difference in behaviour and prognosis. Reliable separation may be challenging, particularly on small and superficial samples. Features in favour of sebaceous carcinoma are the presence of nuclear pleomorphism, atypical mitoses, tumour necrosis and an infiltrative growth pattern. Sebaceoma may also be mistaken for basal cell carcinoma or trichoblastoma, especially if the proportion of mature sebaceous cells is low. Basal cell carcinoma shows more pronounced cytological atypia, numerous apoptotic cells, a peripheral palisade and a stromal cleft artefact. In contrast to sebaceoma, basal cell carcinoma expresses BerEP4 strongly and diffusely [14]. Trichoblastoma typically shows an intimately associated cellular tumour stroma.

Sebaceous carcinoma

Clinical features: Sebaceous carcinoma is a rare tumour with reported incidence rates ranging from 0.5 per million in the black population to 1 per million in Asians and Pacific Islanders and 2 per million in Caucasians [15]. The tumours are traditionally divided by location into periocular and extraocular with the majority of tumours involving the eyelids and the face of elderly patients (median age: 73 years) without gender predilection [15]. Known risk factors include immunosuppression, ultraviolet (UV)-exposure and radiotherapy.

Periocular sebaceous carcinoma accounts for 1.5-5% of eyelid malignancies in Western countries and 30% in India and East Asia [16]. The tumours present as nodules which may

ulcerate. An association with the Meibomian glands is frequent and there is a predilection for the upper eyelid [17].

Extraocular sebaceous carcinoma favours the head and neck area, but the anatomic distribution is wide including the trunk, the extremities and the genitalia. The tumours present as solitary and frequently ulcerated erythematous nodules, reaching several centimetres. Rarely, the tumours arise in a background of a naevus sebaceus [18, 19].

Histological features: The ill-defined, multinodular tumours typically show a diffusely infiltrative growth pattern in dermis and subcutaneous tissues (Fig.4a and b). An epidermal connection is frequently present but a well-circumscribed tumour growth with pushing margins is rare. The tumours are composed predominantly of basaloid polygonal cells with large and irregular vesicular nuclei containing multiple prominent nucleoli (Fig.4c). More mature sebaceous cells with overt sebaceous differentiation in the form of vacuolated pale cytoplasm and atypical scalloped nuclei are admixed in varying proportions (Fig.4c). The degree of cytological atypia can range from mild to severe, and the mitotic activity can be striking including multiple atypical mitoses (Fig.4d). Well-differentiated tumours show overt sebaceous differentiation with a predominance of more mature tumour cells and limited cytological atypia while poorly differentiated tumours are characterized by a sheet-like proliferation of pleomorphic basaloid cells. In poorly differentiated tumours sebaceous differentiation may be difficult to identify morphologically, requiring immunohistochemical confirmation. Tumour necrosis is a common feature, often in the form of comedo-type necrosis (Fig.5a). Rarely, an in-situ component with florid pagetoid spread of tumours cells may be present (Fig.5b). This feature is most frequently observed in periocular tumours. Purely intraepidermal (in situ) sebaceous carcinomas are distinctly rare. Other features

include squamoid metaplasia and the formation of keratin cysts. Lymphovascular and perineural invasion may also be noted (Fig.5c).

Immunohistochemistry: EMA and adipophilin are useful markers in highlighting sebaceous differentiation, particularly in poorly differentiated tumours. Staining is limited to the better differentiated areas of the tumour with more obvious sebaceous differentiation. It is absent in the immature basaloid cells [13]. Tumour cells may also show nuclear staining for factor XIII and GATA3 [20]. The tumour cells express high molecular weight cytokeratins. They are usually positive for CK7 but negative for CK20. P63 and P40 are expressed but BerEP4 is consistently negative.

Behaviour and treatment: Sebaceous carcinoma shows risk for significant morbidity and mortality independent of the anatomical site. Recurrence rates range from 4% to 28%, and the 5-year survival rates range from 70%-97% with a 10-year survival of approximately 79% [16]. Metastatic spread to regional lymph nodes or distant sites involving liver, lung, brain, and bones is seen in 14-25% of patients [21-23]. Poor prognostic features are multicentric origin, concomitant involvement of upper and lower eyelids, poorly differentiated tumours, lymphovascular and orbital invasion, tumour size larger than 10 mm and intraepithelial pagetoid invasion of the overlying epithelium [24-26].

The treatment of choice is wide local excision with consideration for sentinel lymph node biopsy and adjuvant radiation treatment [25]. Orbital exenteration is required in 13 – 23% of periocular sebaceous carcinomas [5].

Differential diagnosis: The diagnosis of sebaceous carcinoma is often challenging. The tumours need to be differentiated from sebaceoma and sebaceous adenoma. Infiltrative margins, nuclear pleomorphism, tumour necrosis and lymphovascular or perineural invasion exclude benign sebaceous neoplasia. Poorly differentiated sebaceous carcinoma may be

difficult to distinguish from basaloid squamous cell carcinoma and basal cell carcinoma. Separation from basaloid squamous cell carcinoma relies on the identification of at least focal sebaceous differentiation morphologically or immunohistochemically. Basal cell carcinoma shows peripheral palisading and retraction artefacts with the surrounding stroma and immunohistochemical expression for BerEp4. Merkel cell carcinoma is a close mimic of poorly differentiated sebaceous carcinoma. It lacks sebaceous differentiation and expresses CK20 and neurofilament protein by immunohistochemistry. Endocrine mucin producing sweat gland carcinoma is well-circumscribed and characterized by a combination of solid, cribriform, cystic and papillary growth patterns. It is composed of basaloid ovoid to epithelioid cells that contain mucin, but cytologic atypia is mild and mitoses are sparse.

Sebaceous tumours associated with Lynch syndrome or hereditary non-polyposis colorectal cancer syndrome (Muir-Torre syndrome)

Sebaceous tumours develop in less than 5% of patients with Lynch syndrome (LS) or hereditary non-polyposis colorectal cancer (HNPCC) syndrome, which has also been referred to as Muir-Torre syndrome (MTS) [3, 27]. The incidence of LS/MTS in patients with sebaceous neoplasms ranges between 14 and 50% [3, 28-32]. The association with LS/MTS is highest for multiple sebaceous tumours and those located outside the head and neck area with onset before age 60 years [2, 6, 33]. Sebaceous adenoma appears to show the strongest association with LS/MTS followed by sebaceoma. The association with sebaceous carcinoma is weakest and relates mainly to extraocular tumours [34]. In contrast, periocular sebaceous carcinomas show no association with LS/MTS. The sebaceous tumours can develop prior to or simultaneously with visceral malignancy. 37-50% of patients with LS/MTS develop two or

more visceral malignancies, more than four visceral malignancies are seen in 10%. Colorectal cancer (usually located from the caecum to splenic flexure) is the most common visceral neoplasia (~50%) followed by cancers of the endometrium, ovary, urothelial tract, upper gastrointestinal tract, pancreas, hepato-biliary tract, prostate and central nervous system (CNS) glioblastoma. Associated findings are adenomatous polyps (~25%) and keratoacanthomas (in at least 20%) which can exhibit sebaceous differentiation [28].

The behaviour of both sebaceous carcinoma and visceral malignancies in the setting of LS/MTS appears to be less aggressive than their sporadic equivalents [28].

Histological features of sebaceous neoplasms associated with LS/MTS: Sebaceous tumours in the setting of LS/MTS can exhibit unusual growth patterns such as a predominantly cystic growth or a keratoacanthoma-like architecture [35]. A solid basaloid growth, adenoid features with mucinous areas, and the presence of different lines of differentiation have also been described.

Immunohistochemistry in sebaceous neoplasms associated with LS/MTS: Loss of expression of one or more of the DNA mismatch repair proteins MLH1, MSH2, MSH6 and PMS2 may be an indicator of underlying Lynch syndrome (Fig.6a-d). Immunohistochemical screening of sebaceous neoplasms can be used as a first-line test when Lynch syndrome is suspected [28, 36-38]. The sensitivity of immunohistochemistry is reported to be 81-85% with a specificity of 48% [29, 36, 39]. Abnormal immunohistochemistry results are not diagnostic of Lynch syndrome and should be interpreted cautiously in conjunction with family history and germline genetic testing. Clinical genetical evaluation is warranted for patients with abnormal immunohistochemical test results and those showing normal immunohistochemical results but a personal or family history of other Lynch syndrome-associated neoplasms, and/or multiple sebaceous neoplasms [36, 40]. Recent studies on the appropriate use of

immunohistochemistry demonstrated that immunohistochemical testing for the mismatch repair proteins to detect an underlying LS/MTS is appropriate in the setting of multiple sebaceous neoplasms, in patients with a history of a MTS-associated tumours or visceral malignancies, in cystic sebaceous tumours and those with a keratoacanthoma-like growth and in patients under 60 years with a single sebaceous neoplasm presenting outside the head and neck area [41, 42].

Molecular aspects in LS/MTS: *MutS Homolog (MSH) 2* and *6*, *MutL Homolog (MLH) 1* and *Postmeiotic Segregation Increased (PMS) 2* are the four DNA mismatch repair (MMR) genes that are affected by a germline mutation in most LS/MTS cases [3]. However, *PMS2* mutation is uncommon. MMR proteins are paired as heterodimers in the cell (MLH1/PMS2 and MSH2/MSH6), hence the loss of the dominant partner (MLH1 or MSH2) affects the stability and presence of the other (PMS2 or MSH6, respectively) (but not vice versa) [43]. *MSH2* is the most frequently mutated gene in LS/MTS (90%) with a large number of mutations described; mutations in exons 5 and 6 seem to be part of a genotype-phenotype correlation with an increased risk for sebaceous tumours [44].

As MMR deficiency is not detected in 35% of LS/MTS cases, this entity has been divided into at least two types. The first and most common type of LS/MTS is a variant of hereditary non-polyposis colorectal cancer that is characterized by defects in MMR genes and early-onset tumours; the other types do not show deficiency in MMR and are related to a biallelic inactivation of *MUTYH* as an autosomal recessive inheritance pattern or other inherited DNA repair defects [45, 46].

The prevalence of MMR-deficiency in sebaceous neoplasms occurs in 15-60%; however, it is not an effective marker as the majority of MMR-deficient sebaceous neoplasms (56-60.5%) does not occur on a background of MMR germline mutation. For example, sebaceous tumours

related to immunosuppression lose the expression of MMR proteins with or without associated germline mutations. Patients with MMR-deficient sebaceous neoplasms but no MMR germline mutation could result from gene hypermethylation, somatic mutation, non-heritable mutation or unidentified germline mutation. Discordance in MMR IHC results in the same patient suggests a sporadic mechanism [29].

Genetic and molecular pathology findings in sebaceous tumours

Somatic MMR-deficiency was found to be responsible for a high proportion (71%) of mutation-carrying sebaceous neoplasms, but an association of *BRAF* and *KRAS* mutations with both sporadic and LS/MTS-associated sebaceous tumours remains controversial [29, 47]. Sebaceous carcinomas appear to be a genetically heterogeneous group with different molecular pathways suggested to be involved in periocular compared to extraocular neoplasms. Extraocular tumours have been reported to harbour mutations in genes affecting DNA repair/chromatin remodelling pathways and somatic mutations in MMR genes with loss of heterozygosity. Contrastingly, periocular tumours display a spectrum of mutations in genes predicted to activate the PI3K signalling cascade [5].

Potentially clinically relevant mutations in sebaceous carcinoma have been reported. In periocular sebaceous carcinoma, two distinct molecular-genetic subtypes have been suggested. The first is defined by somatic mutations in *TP53* and/or *RB1* with concomitant mutation of *NOTCH* genes in tumours presenting in older patients with frequent local recurrence [48]. The second subtype is characterized by transcriptionally active high-risk human papillomavirus (HPV). These tumours arise in younger patients and have not resulted in local recurrence. In the Asian patient population, no mutations have been detected in *KRAS*, *NRAS*,

BRAF, *PIK3CA* or MMR genes, suggesting an altogether different molecular pathway [49]. Similarly, the presence of HPV genome seems to be rare in periocular sebaceous carcinoma in Asia. Furthermore, three distinct molecular and clinical settings have recently been identified: 1. Sebaceous carcinoma with microsatellite instability (MSI), 2. Sebaceous carcinoma with UV-damage-associated mutational signatures and 3. Sebaceous carcinoma showing a paucity of somatic mutations [50]. Histologically, tumours associated with UV-damage are poorly differentiated with an infiltrative growth pattern compared to tumours with the MSI signature. Pauci-mutational sebaceous carcinoma occurs exclusively on the face. All three classes of sebaceous carcinoma acquire recurrent mutations, including *NOTCH1* gene in extraocular sebaceous carcinoma, *ZNF750* gene in pauci-mutational periocular sebaceous carcinoma and the *RREB1* gene in sebaceous carcinoma with MSI. These findings support the theory that specific somatic alterations or the epigenetic state of the cell of origin underlie distinct mechanisms of sebaceous carcinoma tumorigenesis [50].

Finally, few studies have been performed at the RNA level and although some novel aberrant miRNAs and IncRNAs have been suggested to play a role this landscape is yet to be fully explored [4, 51-53]. Large scale molecular studies will help to elucidate the role of germline and somatic variations in the disease pathogenesis.

Conclusion

The correct diagnosis and classification of sebaceous neoplasms is important not only to predict behaviour but also as a potential sentinel feature raising concern for underlying Lynch syndrome. While diagnostic and prognostic information still depends largely on histological criteria, an improved understanding of the underlying molecular pathways may lead to more robust diagnosis and prediction of behaviour in the future.

References

1. Flux K. Sebaceous neoplasms. *Surg Pathol Clin* 2017;**10**;367-382.
2. Lazar AJ, Lyle S, Calonje E. Sebaceous neoplasia and torre-muir syndrome. *Curr Diagn Pathol* 2007;**13**;301-319.
3. Marcoval J, Talavera-Belmonte A, Fornons-Servent R, Bauer-Alonso A, Penin RM, Servitje O. Cutaneous sebaceous tumours and lynch syndrome: Long-term follow-up of 60 patients. *Clin Exp Dermatol* 2019;**44**;506-511.
4. Tetzlaff MT, Curry JL, Yin V *et al.* Distinct pathways in the pathogenesis of sebaceous carcinomas implicated by differentially expressed micrornas. *JAMA Ophthalmol* 2015;**133**;1109-1116.
5. Tetzlaff MT, Singh RR, Seviour EG *et al.* Next-generation sequencing identifies high frequency of mutations in potentially clinically actionable genes in sebaceous carcinoma. *J Pathol* 2016;**240**;84-95.
6. Shalin SC, Lyle S, Calonje E, Lazar AJ. Sebaceous neoplasia and the muir-torre syndrome: Important connections with clinical implications. *Histopathology* 2010;**56**;133-147.
7. Harvey NT, Tabone T, Erber W, Wood BA. Circumscribed sebaceous neoplasms: A morphological, immunohistochemical and molecular analysis. *Pathology* 2016;**48**;454-462.
8. Bourlond F, Velter C, Cribier B. Clinicopathological study of 47 cases of sebaceoma. *Ann Dermatol Venereol* 2016;**143**;814-824.
9. Ansai S, Kimura T. Rippled-pattern sebaceoma: A clinicopathological study. *Am J Dermatopathol* 2009;**31**;364-366.
10. Wiedemeyer K, Kyrpychova L, Isikci OT *et al.* Sebaceous neoplasms with rippled, labyrinthine/sinusoidal, petaloid, and carcinoid-like patterns: A study of 57 cases

validating their occurrence as a morphological spectrum and showing no significant association with muir-torre syndrome or DNA mismatch repair protein deficiency. *Am J Dermatopathol* 2018;**40**;479-485.

11. Kazakov DV, Kutzner H, Rutten A, Mukensnabl P, Michal M. Carcinoid-like pattern in sebaceous neoplasms: Another distinctive, previously unrecognized pattern in extraocular sebaceous carcinoma and sebaceoma. *Am J Dermatopathol* 2005;**27**;195-203.
12. Flux K, Kutzner H, Rutten A *et al.* Infundibulocystic structures and prominent squamous metaplasia in sebaceoma-a rare feature. A clinicopathologic study of 10 cases. *Am J Dermatopathol* 2016;**38**;678-682.
13. Ostler DA, Prieto VG, Reed JA, Deavers MT, Lazar AJ, Ivan D. Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: An immunohistochemical study of 117 cases. *Mod Pathol* 2010;**23**;567-573.
14. Fan YS, Carr RA, Sanders DS, Smith AP, Lazar AJ, Calonje E. Characteristic ber-ep4 and ema expression in sebaceoma is immunohistochemically distinct from basal cell carcinoma. *Histopathology* 2007;**51**;80-86.
15. Dasgupta T, Wilson LD, Yu JB. A retrospective review of 1349 cases of sebaceous carcinoma. *Cancer* 2009;**115**;158-165.
16. Haber R, Battistella M, Pages C, Bagot M, Lebbe C, Basset-Seguin N. Sebaceous carcinomas of the skin: 24 cases and a literature review. *Acta Derm Venereol* 2017;**97**;959-961.
17. Rao NA, Hidayat AA, McLean IW, Zimmerman LE. Sebaceous carcinomas of the ocular adnexa: A clinicopathologic study of 104 cases, with five-year follow-up data. *Hum Pathol* 1982;**13**;113-122.

18. Izumi M, Tang X, Chiu CS *et al.* Ten cases of sebaceous carcinoma arising in nevus sebaceus. *J Dermatol* 2008;**35**;704-711.
19. Kazakov DV, Calonje E, Zelger B *et al.* Sebaceous carcinoma arising in nevus sebaceus of jadassohn: A clinicopathological study of five cases. *Am J Dermatopathol* 2007;**29**;242-248.
20. Tjarks BJ, Pownell BR, Evans C *et al.* Evaluation and comparison of staining patterns of factor xiiia (ac-1a1), adipophilin and gata3 in sebaceous neoplasia. *J Cutan Pathol* 2018;**45**;1-7.
21. Esmaeli B, Nasser QJ, Cruz H, Fellman M, Warneke CL, Ivan D. American joint committee on cancer t category for eyelid sebaceous carcinoma correlates with nodal metastasis and survival. *Ophthalmology* 2012;**119**;1078-1082.
22. Erovic BM, Goldstein DP, Kim D *et al.* Sebaceous gland carcinoma of the head and neck: The princess margaret hospital experience. *Head Neck* 2013;**35**;316-320.
23. Tripathi R, Chen Z, Li L, Bordeaux JS. Incidence and survival of sebaceous carcinoma in the united states. *J Am Acad Dermatol* 2016;**75**;1210-1215.
24. Sa HS, Rubin ML, Xu S *et al.* Prognostic factors for local recurrence, metastasis and survival for sebaceous carcinoma of the eyelid: Observations in 100 patients. *Br J Ophthalmol* 2019;**103**;980-984.
25. Tryggvason G, Bayon R, Pagedar NA. Epidemiology of sebaceous carcinoma of the head and neck: Implications for lymph node management. *Head Neck* 2012;**34**;1765-1768.
26. Chao AN, Shields CL, Krema H, Shields JA. Outcome of patients with periocular sebaceous gland carcinoma with and without conjunctival intraepithelial invasion. *Ophthalmology* 2001;**108**;1877-1883.

27. Schwartz RA, Torre DP. The muir-torre syndrome: A 25-year retrospect. *J Am Acad Dermatol* 1995;**33**;90-104.
28. Ponti G, Losi L, Di Gregorio C *et al.* Identification of muir-torre syndrome among patients with sebaceous tumors and keratoacanthomas: Role of clinical features, microsatellite instability, and immunohistochemistry. *Cancer* 2005;**103**;1018-1025.
29. Roberts ME, Riegert-Johnson DL, Thomas BC *et al.* Screening for muir-torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms. *J Genet Couns* 2013;**22**;393-405.
30. Roberts ME, Riegert-Johnson DL, Thomas BC *et al.* A clinical scoring system to identify patients with sebaceous neoplasms at risk for the muir-torre variant of lynch syndrome. *Genet Med* 2014;**16**;711-716.
31. Lee BA, Yu L, Ma L, Lind AC, Lu D. Sebaceous neoplasms with mismatch repair protein expressions and the frequency of co-existing visceral tumors. *J Am Acad Dermatol* 2012;**67**;1228-1234.
32. Everett JN, Raymond VM, Dandapani M *et al.* Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm. *JAMA Dermatol* 2014;**150**;1315-1321.
33. Singh RS, Grayson W, Redston M *et al.* Site and tumor type predicts DNA mismatch repair status in cutaneous sebaceous neoplasia. *Am J Surg Pathol* 2008;**32**;936-942.
34. Dores GM, Curtis RE, Toro JR, Devesa SS, Fraumeni JF, Jr. Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: Insight into muir-torre syndrome. *Cancer* 2008;**113**;3372-3381.

35. Rutten A, Burgdorf W, Hugel H *et al.* Cystic sebaceous tumors as marker lesions for the muir-torre syndrome: A histopathologic and molecular genetic study. *Am J Dermatopathol* 1999;**21**;405-413.
36. Jessup CJ, Redston M, Tilton E, Reimann JD. Importance of universal mismatch repair protein immunohistochemistry in patients with sebaceous neoplasia as an initial screening tool for muir-torre syndrome. *Hum Pathol* 2016;**49**;1-9.
37. Cesinaro AM, Ubiali A, Sighinolfi P, Trentini GP, Gentili F, Facchetti F. Mismatch repair proteins expression and microsatellite instability in skin lesions with sebaceous differentiation: A study in different clinical subgroups with and without extracutaneous cancer. *Am J Dermatopathol* 2007;**29**;351-358.
38. Chhibber V, Dresser K, Mahalingam M. Msh-6: Extending the reliability of immunohistochemistry as a screening tool in muir-torre syndrome. *Mod Pathol* 2008;**21**;159-164.
39. Kim RH, Nagler AR, Meehan SA. Universal immunohistochemical screening of sebaceous neoplasms for muir-torre syndrome: Putting the cart before the horse? *J Am Acad Dermatol* 2016;**75**;1078-1079.
40. Ollila S, Fitzpatrick R, Sarantaus L *et al.* The importance of functional testing in the genetic assessment of muir-torre syndrome, a clinical subphenotype of hnpcc. *Int J Oncol* 2006;**28**;149-153.
41. Task Force/Committee M, Vidal CI, Sutton A *et al*. Muir-torre syndrome appropriate use criteria: Effect of patient age on appropriate use scores. *J Cutan Pathol* 2019;**46**;484-489.

42. Vidal CI, Armbrect EA, Andea AA *et al*. Appropriate use criteria in dermatopathology: Initial recommendations from the american society of dermatopathology. *J Cutan Pathol* 2018;**45**;563-580.
43. Geiersbach KB, Samowitz WS. Microsatellite instability and colorectal cancer. *Arch Pathol Lab Med* 2011;**135**;1269-1277.
44. John AM, Schwartz RA. Muir-torre syndrome (mts): An update and approach to diagnosis and management. *J Am Acad Dermatol* 2016;**74**;558-566.
45. Perera S, Ramyar L, Mitri A *et al.* A novel complex mutation in msh2 contributes to both muir-torre and lynch syndrome. *J Hum Genet* 2010;**55**;37-41.
46. Ponti G, Ponz de Leon M, Maffei S *et al.* Attenuated familial adenomatous polyposis and muir-torre syndrome linked to compound biallelic constitutional myh gene mutations. *Clin Genet* 2005;**68**;442-447.
47. Cornejo KM, Hutchinson L, Deng A *et al.* Braf/kras gene sequencing of sebaceous neoplasms after mismatch repair protein analysis. *Hum Pathol* 2014;**45**;1213-1220.
48. Tetzlaff MT, Curry JL, Ning J *et al.* Distinct biological types of ocular adnexal sebaceous carcinoma: Hpv-driven and virus-negative tumors arise through nonoverlapping molecular-genetic alterations. *Clin Cancer Res* 2019;**25**;1280-1290.
49. Kwon MJ, Nam ES, Cho SJ *et al.* Mutation analysis of ctnnb1 gene and the ras pathway genes kras, nras, braf, and pik3ca in eyelid sebaceous carcinomas. *Pathol Res Pract* 2017;**213**;654-658.
50. North JP, Golovato J, Vaske CJ *et al.* Cell of origin and mutation pattern define three clinically distinct classes of sebaceous carcinoma. *Nat Commun* 2018;**9**;1894.

51. Bhardwaj M, Sen S, Chosdol K *et al.* Mirna-200c and mirna-141 as potential prognostic biomarkers and regulators of epithelial-mesenchymal transition in eyelid sebaceous gland carcinoma. *Br J Ophthalmol* 2017;**101**;536-542.
52. Bladen JC, Wang J, Sangaralingam A *et al.* Microrna and transcriptome analysis in periocular sebaceous gland carcinoma. *Sci Rep* 2018;**8**;7531.
53. Song X, Fan J, Jia R *et al.* Identification and regulation pattern analysis of long noncoding rnas in meibomian gland carcinoma. *Epigenomics* 2019;**11**;381-400.

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Figure legends

Figure 1. Sebaceous Adenoma: The tumour is well circumscribed and symmetrical with multifocal epidermal connection. Also note the areas of epidermal ulceration (a). The centre of the tumour is composed of mature sebaceous cells characterized by a bubbly cytoplasm and centrally located indented, 'scalloped' nuclei. No cytological atypia is observed (b). In the periphery of the tumour lobules there is an expanded germinative cell layer composed of basaloid polygonal cells with vesicular nuclei and eosinophilic nucleoli (c). A keratoacanthoma-like tumour growth with cystic features may be observed (d).

Figure 2. Sebaceoma: This basaloid tumour shows a multinodular growth with multifocal epidermal connection (a). It is composed of sheets of basaloid epithelioid polygonal cells with little cytoplasm containing vesicular nuclei with eosinophilic nucleoli. In the upper left corner, the tumour cells show maturation and contain lipid vacuoles. Also note the lack of nuclear pleomorphism (b). Clusters of mature sebaceous cells are intermingled with the basaloid germinative tumour cells (c). Areas of holocrine secretion may resemble tumour necrosis (d). Sebaceous duct differentiation is present (e). The tumour cells are arranged in narrow ribbons, giving rise to a sinusoidal growth pattern (f).

Figure 3. Sebaceoma: Infundibular keratocysts may be encountered within the tumour (a). Cystic (b) and keratoacanthoma-like growth (c) patterns are rarely encountered. Immunohistochemical staining for adipophilin highlights the mature sebaceous cells (d).

Figure 4. Sebaceous carcinoma: This large multinodular basaloid tumour invades deeply (a) with invasion of skeletal muscle (b). The tumour is composed predominantly of basaloid

cells with scattered admixed lipid containing cells resembling mature sebaceous cells. Also note the degree of cytological atypia (c). There is marked nuclear pleomorphism and atypical mitotic activity (d).

Figure 5. Sebaceous carcinoma: Comedo necrosis is shown here (a). There is involvement of the overlying epidermis by malignant sebaceous tumour cells in a Pagetoid arrangement (b). Perineural infiltration (c).

Figure 6. Immunohistochemistry for the mismatch repair proteins: This sebaceoma from a patient with Lynch syndrome shows retained immunohistochemical expression of MLH1 (a) and PMS2 (b). MSH2 (c) and MSH6 (d) expression is lost.

Figures

Figure 1.

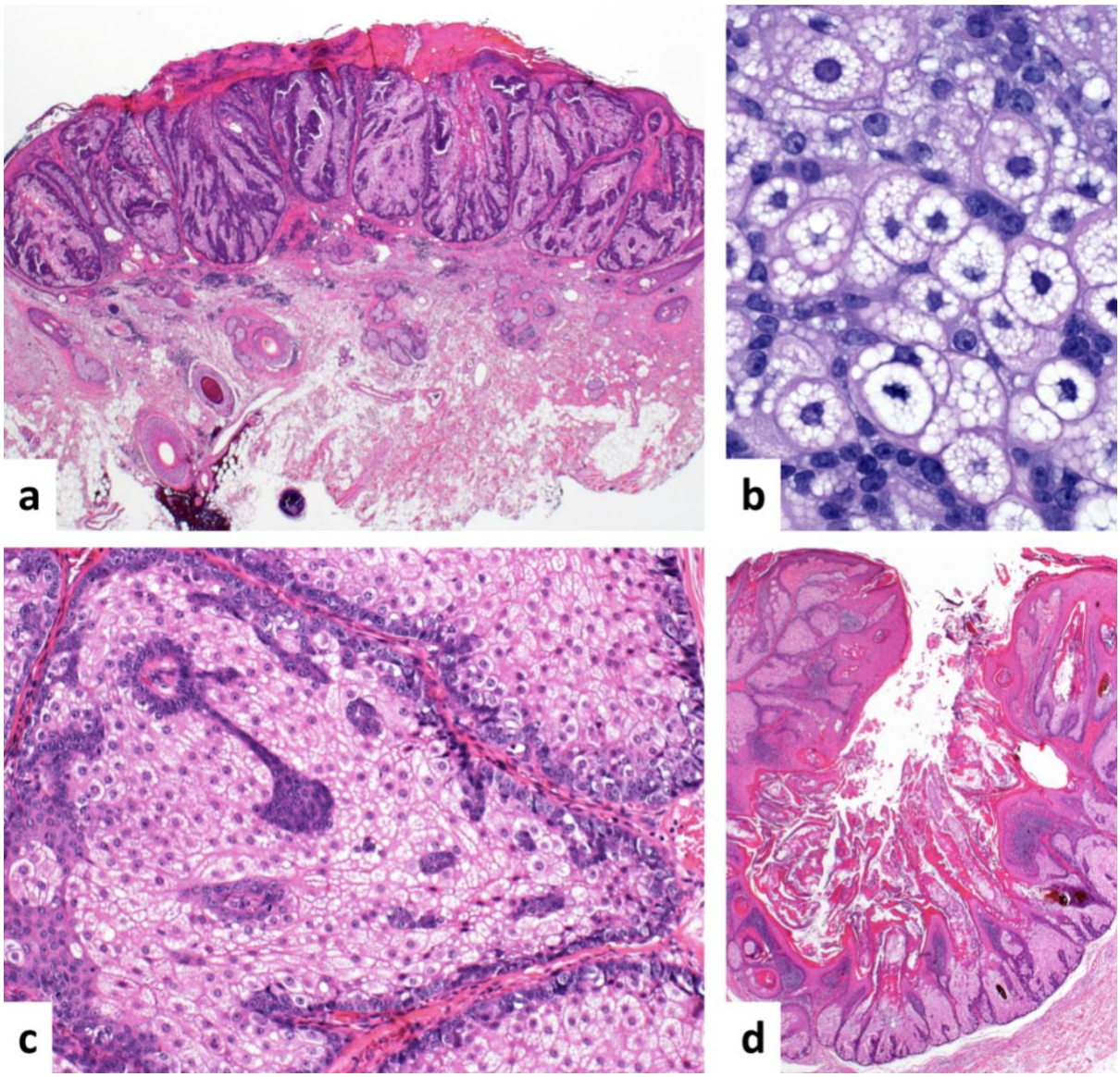

Figure 2.

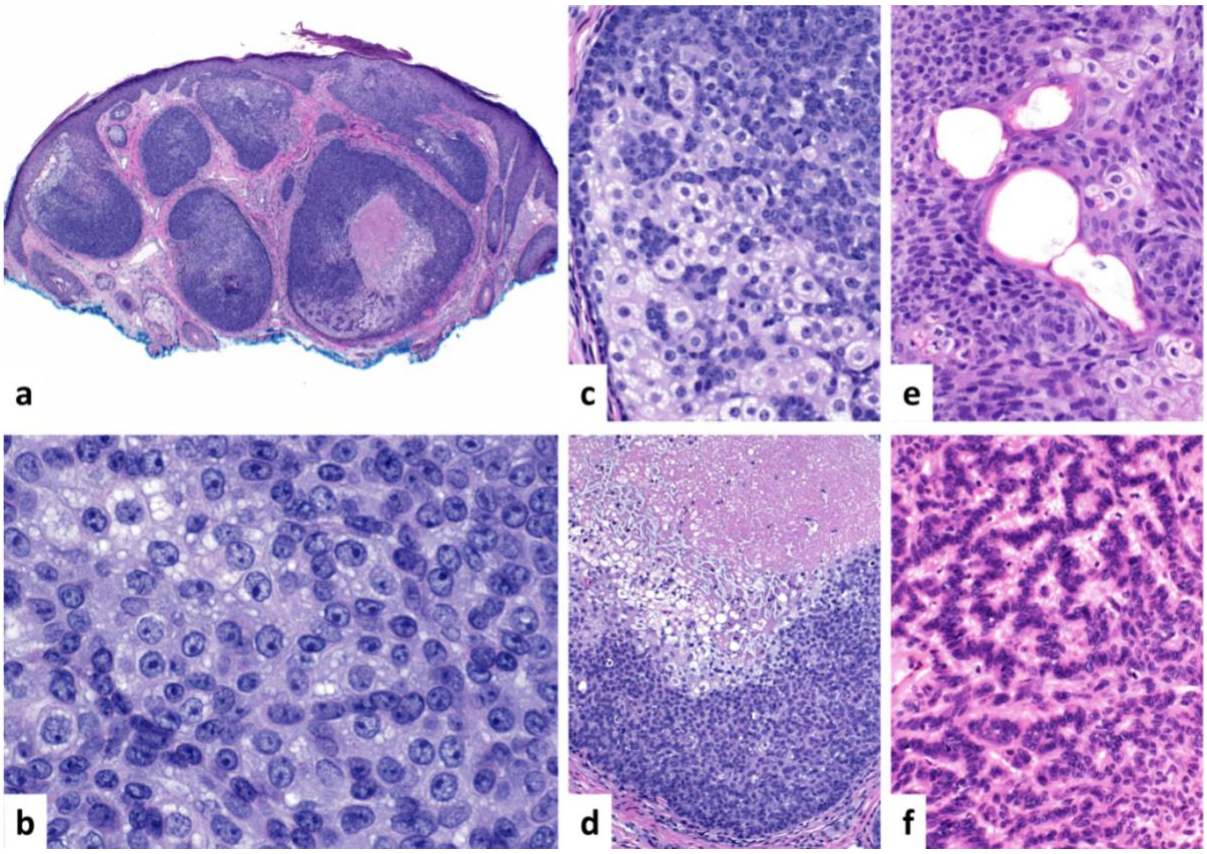

Figure 3.

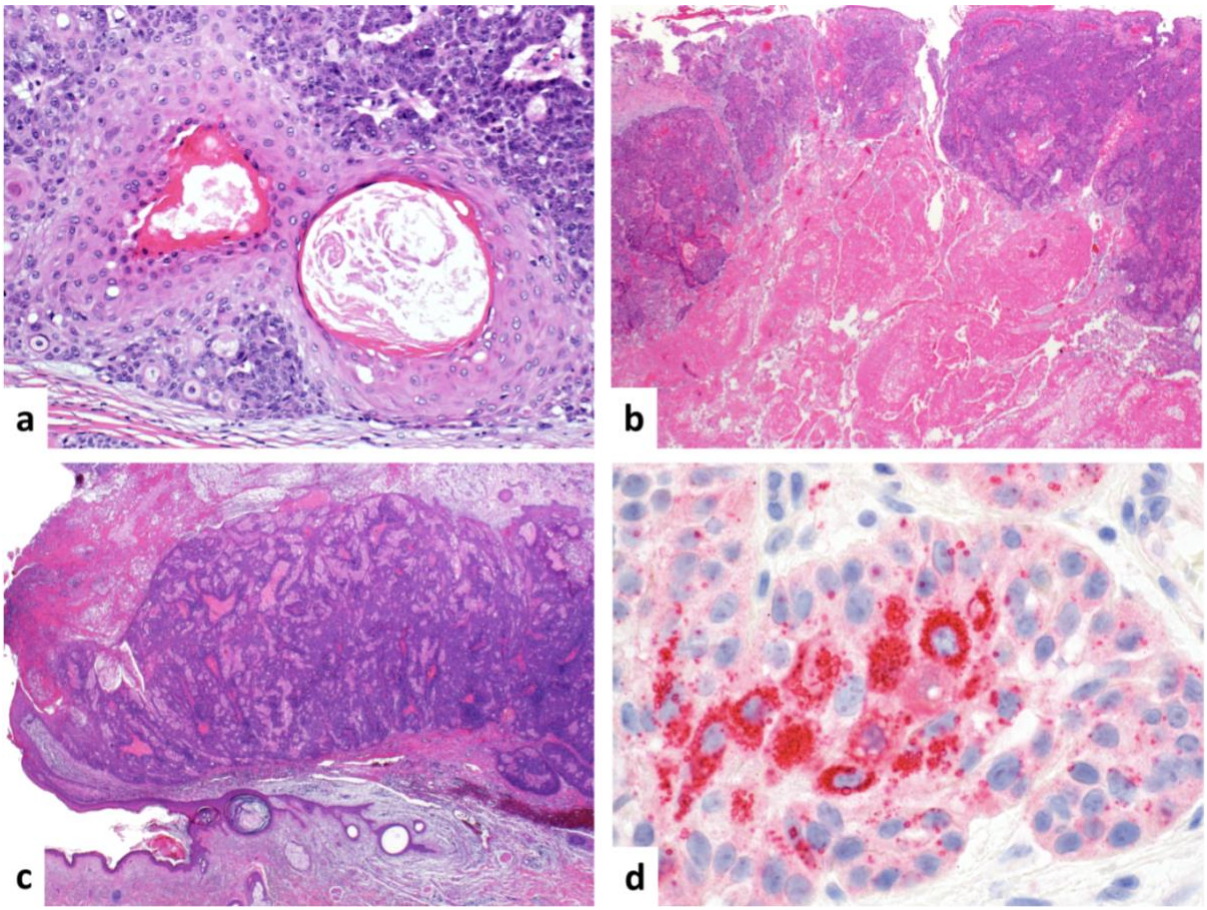

Figure 4.

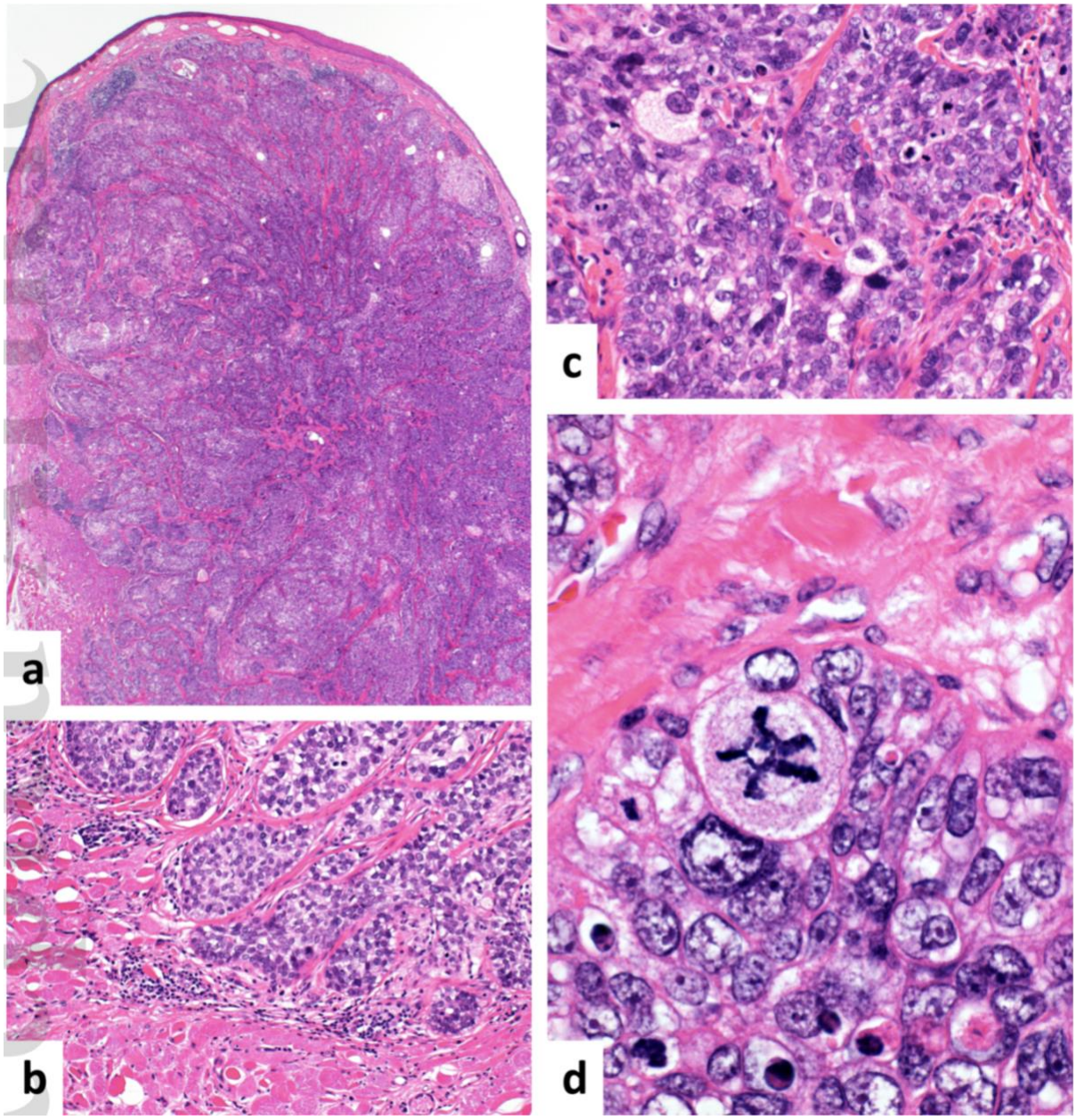

Figure 5.