CUTANEOUS NEOPLASIA OF THE HEAD AND NECK

A selective review

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Introduction

The head and neck area has disproportionate number of cutaneous tumors given the surface area, as compared with the rest of the body. Many of the tumors are related to chronic actinic damage and the most common by far are squamous and basal cell carcinomas.

A number of tumors are present predominantly or exclusively in the head and neck area of the skin. These include syringomas, cylindromas, trichoepitheliomas, mucinous carcinoma and cutaneous angiosarcomas among others. I present a review of three neoplasms that are found in the head of individuals that present particularly troublesome histological diagnosis. Their knowledge, biological behavior, and differential diagnoses pose considerable difficulty to pathologists.

ATYPICAL FIBROXANTHOMA (AFX)

Atypical fibroxanthoma refers to a group of usually indolent cutaneous tumors that occur in older adults and are characterized histologically by a population of fusiform, epithelioid, and pleomorphic cells, numerous cells in mitosis, and intracytoplasmic lipidization in some cells. Although it was recognized previously, Fretzin and Helwig described 140 cases and popularized the term atypical fibroxanthoma. Several large series have been described through the years refining the knowledge of AFX. Some authors regard AFX as a superficial variant of malignant fibrous histiocytoma. In fact, the whole concept of malignant fibrous histiocytomas has been challenged. These neoplasms have been reinterpreted as having pleomorphic myofibroblastic differentiation.
Clinically, atypical fibroxanthoma presents most often as a rapidly enlarging or exophytic polyp that is usually solitary and occurs on the head or neck region of older adults. Ulceration is uncommon. Rarely, other sites may be involved. Most patients have a long history of sun exposure; antecedent trauma has been reported in a few cases. There is also said to be a younger age group whose lesions are located typically on non-sun-exposed areas, but these neoplasms may represent benign fibrous histiocytomas (dermatofibromas) with pleomorphic cells. Atypical fibroxanthomas range in size from 1 to >6cm in diameter, but most lesions are 1 to 2cm. If intact, the skin overlying the lesion is smooth and may reflect a yellow hue. The clinical differential diagnosis is with squamous carcinoma, malignant melanoma, and lobular hemangioma (pyogenic granuloma). Local excision is curative in most cases. The superficial lesions rarely recur; a few reported cases have metastasized, but the diagnostic criteria used to identify those neoplasms were not always convincing. Some authors would go as far as to support that any “metastasizing” AFX is not an AFX at all but an MFH.

Histologically, atypical fibroxanthoma may have symmetric or asymmetric profile. The borders are usually circumscribed, but may be infiltrative laterally. Polypoid lesions may have a peripheral collarette of squamous or adnexal epithelium. Some lesions have a Grenz zone but most lesions abut upon the epidermis, which may be eroded or ulcerated. Some lesions extend into the superficial subcutis but only to a very limited degree. The deeper aspects may be bordered by a mononuclear inflammatory infiltrate. The architectural growth patterns of the
tumors may be haphazard, storiform, or fascicular. The stroma is reticulin rich. There are inconspicuous to ectatic capillaries throughout the lesions; some may contain areas of hemorrhage, but necrosis is absent. Vascular and perineural invasion are not present; if identified, a more aggressive lesion should be suspected. Factors related to aggressive behavior and metastasis are vascular invasion, recurrence, deep tissue invasion, tumor necrosis and, possibly, defective or depressed host resistance. Most authors nowadays would not accept subcutaneous spread, vascular invasion or necrosis within the spectrum of atypical fibroxanthoma.

The tumor cells have a continuous cytological range from predominantly fusiform to round, with or without various admixtures of giant cells. The cell cytoplasm is usually abundant and eosinophilic to amphophilic. Many cells may be filled with microvesicular lipid, which is easily detected with oil-red-O. The nuclei display wide variations in size and shape, none to several prominent nucleoli may be found, and nuclei may resemble Reed–Sternberg cells (Figure 1). Typical and atypical (multipolar) mitotic figures are observed; the mitotic index is in the range of one per high-power field. Multinucleated giant cells within the lesion may have monomorphic and/or pleomorphic nuclei. Occasionally, Touton type giant cells are present. Many cases are almost entirely monomorphic spindle cells with fascicular arrangement and even desmoplastic in nature (Figure 2). Rare cases contain osteoclast-like giant cells. A clear-cell variant (Figure 3), granular cell variant, myxoid changes, lesions with keloidal collagen, and a “pigmented”
hemosiderotic variant have been described. We have seen several examples of angiomatoid or aneurysmal AFX.

Immunohistochemically, the cells of atypical fibroxanthoma are virtually always positive for vimentin, HAM56, α1-antichymotrypsin, α 1-antitrypsin, and cathepsin B, although these antigens are largely non-specific. The use of CD117 has been proposed as a marker for AFX, although the results were disputed. CD10 stains AFX uniformly and it is an useful marker\textsuperscript{4, 5}. CD99 is another cytoplasmic marker that stains AFX\textsuperscript{6}. Some authors believe that it can discriminate between AFX and MFH\textsuperscript{7}. About half of the lesions mark to some degree with actin antibodies. S-100 protein, melan A, desmin, and the cytokeratins are negative. Often, S-100-positive dendritic, non-neoplastic cells may be present within these lesions. At times they can be so numerous as to lead to a misdiagnosis of melanoma.

Ultrastructurally, the cells have abundant cytoplasm with filopodia, numerous lysosomes with phagocytosed material, lipid vacuoles, and variable amounts of intracytoplasmic filaments. There is no basal lamina, nor are there pinocytotic vesicles or diagnostic inclusion bodies. Rare cases have contained cells with cytoplasmic Langerhans-like granules, which are probably non-neoplastic Langerhans cells admixed with the tumor.

DNA analysis by flow cytometry has shown mostly diploid DNA in atypical fibroxanthoma, in contrast with malignant fibrous histiocytomas, which are usually aneuploid. However, DNA image analysis has identified aneuploid cells in all cases of atypical fibroxanthoma, suggesting that histologic identification of
pleomorphic cells correlates highly with the aneuploid areas of atypical fibroxanthoma.

The main differential diagnoses are with spindle cell squamous carcinoma, malignant melanoma, leiomyosarcoma, and malignant fibrous histiocytoma, all of which may be similar on regular histology. Aside from any epidermal or junctional component, squamous carcinoma can be differentiated by its positivity for cytokeratins, melanoma can be differentiated with S-100 protein and, less often, melan A, and leiomyosarcoma can be differentiated by extensive desmin positivity or ultrastructural attributes. Immunohistochemical stains are not without peril. We have seen cross reactivity or spurious staining occasionally. The most common culprits are keratin and actin antibodies. Interestingly, a “misdiagnosis” may carry little consequence for the patient’s health, since spindle cell squamous cell carcinoma, AFX and superficial leiomyosarcomas are relatively indolent neoplasms. Pleomorphic sarcomas, often regarded as malignant fibrous histiocytoma, can be differentiated by the knowledge of the complete clinical context. Deeper soft tissue lesions on occasion may extend into the dermis. As a general rule, sarcomas of the dermis and superficial subcutis are relatively indolent, including those with pleomorphic cytology, while deeper tumors should be regarded as more aggressive. The diagnosis of AFX in those cases carries substantial risk. Thus, a superficial biopsy that does not sample the lesion entirely, should not be considered diagnostic or prognostic of its biological potential. Dermatofibrosarcoma protuberans can be excluded because of its characteristically monomorphous cytology, cartwheel pattern and positivity for
CD34. Malignant giant cell tumor can be excluded because it has osteoclastic giant cells with bland cytology admixed with pleomorphic mononuclear cells, although some have classified these, in superficial locations, as atypical fibroxanthoma. Reticulohistiocytoma can be differentiated by its uniform population of epithelioid cells with abundant “ground glass” cytoplasm and lack of cytological pleomorphism.

**MERKEL CELL (NEUROENDOCRINE) CARCINOMA (MCC)**

Cutaneous neuroendocrine carcinoma is characterized by a spectrum of small blue cell tumors that are found usually within the dermis. They have histologic features of epithelial cells and neuroendocrine cells. A new virus called the Merkel Cell Polyomavirus (MCPyV) has recently been found in Merkel Cell Carcinoma. The MCPyV is closely related to a latent polyomavirus found in African green monkeys, unlike the four other known human polyomaviruses, which belong to the simian virus 40 (SV40) subgroup\(^8\,10\). Merkel cell carcinoma most commonly arises in the elderly and has a predilection for the upper body, although the trunk and lower limbs may be involved. The clinical differential diagnosis is non-specific. The prognosis of the tumors has been variable; data correlating tumor size and depth to clinical outcome is mostly empirical to date. In more recent years accumulated data have suggested that, overall, these are aggressive tumors with a tendency to repeated recurrence and eventual metastasis in most cases.
Data from NCI’s SEER (Surveillance, Epidemiology, and End Results) Program from 1973 to 2006, contained demographics and survival of 3870 cases of MCC. The incidence was higher in men (2380 cases, 61.5%) than in women (1490 cases, 38.5%). Most patients were white (94.9%) between 60 and 85 years of age. MCC was rare in blacks. The most common location was the head and neck. The salivary glands, nasal cavity, lip, lymph nodes, vulva, vagina and esophagus were the most common extracutaneous sites. The 10-year relative survival rate was higher in women than men (64.8% vs. 50.5%, p < 0.001). Patients aged 50-69 years had the highest 10-year relative survival rate (59.6%). Stage of disease was the best predictor of survival. Histologically, one may observe a range of trabecular to insular or diffuse growth patterns, any or all of which may coexist within an individual tumor (Figure 4). The lesion often fills the dermis, usually with sparing of the epidermis by a thin Grenz zone. Uncommon findings include epidermal involvement (Figure 5), association with keratinocyte pleomorphism similar to Bowen’s disease, squamoid areas (Figure 6), clear cell areas, and ductal components. Cytologically, the tumor cells typically are monomorphic. The cytoplasm is usually scant to almost non apparent and is amphophilic to eosinophilic. The nuclei are relatively uniform, grayish and may exhibit nuclear molding, similar to visceral small cell carcinomas. However, in contrast with most cases of the latter, the cells in cutaneous neuroendocrine carcinomas are readily discernable, often lacking crush artifact. The chromatin pattern is finely granular and “dusty”; small nucleoli may be observed.
Histochemically, silver stains are usually negative, corresponding to the paucity of neurosecretory granules in the tumor cells. Immunohistochemically, a frequent pattern is often observed; this consists of paranuclear “dot-like” condensations of filaments which are positive for low molecular weight keratins such as AE1/AE3, CAM 5.2, or cytokeratin 20. Some tumors have a peripheral membrane-like staining. Mixed staining patterns are seen. The cytokeratin 20 positivity is a valuable discriminant from other types of small cell carcinoma. However CK20 negative and CK7 positive MCC have been reported\textsuperscript{12}. EMA (epithelial membrane antigen), NSE (neuron-specific enolase), neurofilament, chromogranin, synaptophysin and BER-EP4 also are positive in most tumors. MCC may also be positive for CD99, CD117, and TdT. S-100 protein, CEA, and lymphocyte markers are consistently negative.

Merkel cell carcinomas are usually negative for TTF-1 in contrast to the majority of pulmonary and a subset of extrapulmonary (noncutaneous) neuroendocrine carcinomas\textsuperscript{13,14}. Dual staining of CK20-D2 40 demonstrates lymphatic invasion.

Ultrastructurally, the tumor cells are joined to each other by macula adherens-type junctions. Characteristic paranuclear filaments arranged in circular aggregates are seen, and 80–120nm neurosecretory granules are also observed in properly fixed specimens.

The histologic differential diagnosis is usually limited, but includes small cell malignant melanoma, cutaneous lymphoma, neuroendocrine basal cell carcinoma (rarely), metastatic small cell carcinoma, and Ewing’s sarcoma.
Among these, distinction from metastatic small cell carcinoma is often the most difficult and, as always, it is advisable to check the clinical history carefully and suggest a least a chest radiograph.

MICROCYSTIC ADNEXAL CARCINOMA (MAC)

This is an infiltrative tumor composed of small cysts, ducts, and strands of basaloid cells within a fibrotic stroma described by Goldstein, Barr, and Santa Cruz in 1982. Clinically, the lesion occurs most often on the face of an adult. It is usually a skin-colored, indurated plaque, but may be tumefactive. The lesion is usually locally aggressive and local excision may be curative, provided the tumor is removed completely. Distant metastatic disease may occur albeit very rarely.

A study using Surveillance, Epidemiology, and End Results (SEER) Database on 223 patients with MAC provide its clinical profile. The tumor was present on the head and neck area in 74% of the cases. The median age was 68 years. There was a slight female predominance: 43% M-57%F. Ninety percent of the patients were white. Seventy four percent were localized to the dermis, 7% extended into the subcutaneous tissue and 9% invaded soft tissue, muscle or bone. Three cases have lymph node metastases and one patient presented with distant metastases. The 10 year survival was 86% with a matched US population survival of 97.7%, indicating a normal life span.
Two histological variants have been described. Lesions with small keratinizing cysts and solid epithelial strands that is known as microcystic adnexal carcinoma and tumors with prominent glandular components known as “sclerosing sweat duct carcinoma or malignant syringoma”. It must noted that many neoplasms contain both components, usually with predominance of one type.

Histologically, the tumor has a stratified histology from the epidermis to the deep dermis. Microkeratocysts are usually observed in the superficial portion. Solid strands of basaloïd cells alternate with the cysts (Figure 7); some of these may harbor ducts and zones of microcalcification, although some lesions may have prominent lumina, solid cords (Figure 8), clear cell changes, and arborizing tubules. In the mid-dermis, the basaloïd strands and ducts are dominant while the microkeratocysts are diminished. In addition to ducts, some cases contain sebocytes. In the deeper portions, the stroma is typically more desmoplastic and the epithelial elements may diminish to small clusters of two to three cells. Often the subcutaneous tissue and skeletal muscle are infiltrated. Perineural invasion is almost the rule and it is more evident in the deeper dermis (Figure 9).

Cytologically, most lesions contain cells of relatively uniform size; few cells, if any, are seen in mitosis. A higher grade lesion with similar histologic features has been described\textsuperscript{18}. Too few of these carcinomas have been studied to be able to compare with the classical MAC.

The ductal variant has many ductal structures with a syringoma-like appearance. The ducts branch and anastomose and there is a dense fibrous stroma. The ducts have bland cytological features and may present areas of clear cytoplasm
very similar to the clear cell syringoma. Others may have a small cystic appearance lined by ductal epithelium. Furthermore, some areas have intraluminal papillations resembling decapitation secretion of apocrine glands. It must be pointed however, that these are ductal structures and not secretory epithelium.

Immunohistochemically, these lesions express CEA in the gland lumina, and a variety of cytokeratins, but they lack CD34 staining of the stroma, a point which may help differentiate them from desmoplastic trichoepithelioma (which may contain CD34+ stroma) in some cases.

The differential diagnosis is with desmoplastic trichoepithelioma, morpheic basal cell carcinoma, metastatic breast carcinoma, plaque type syringoma\textsuperscript{19}, and papillary eccrine adenoma depending on the tumor differentiation\textsuperscript{20}.

**Conclusions**

Benign and malignant cutaneous neoplasms are very common in the head and neck region. Actually, some of them have preferential or almost exclusive incidence in this area.

Atypical fibroxanthoma presents complicated differential diagnoses and a currently uncertain nosologic and conceptual dilemma.

Merkel cell carcinoma is a rare but increasing oncological problem. It resembles the Merkel cell, a keratinocyte derived cell with neuroendocrine features but unknown functions. Its diagnosis carries a relatively less ominous prognosis than earlier suspected.
Finally, microcystic adnexal carcinoma is a locally aggressive low grade adnexal carcinoma that poses a complicated differential diagnoses but has a good prognosis.
REFERENCES


Figure 1

Atypical fibroxanthoma. Classical pleomorphic cytology
Figure 2

Atypical fibroxanthoma. Desmoplastic non pleomorphic type. Rare areas contained more atypical cytology.
Figure 3

Atypical fibroxanthoma. Clear cell type. Note the alveolar arrangement and epithelioid cytology.
Figure 4
Merkel cell carcinoma. Classical solid histology. There is nuclear crowding with nearly absent cytoplasm
A) Intraepidermal Merkel cell carcinoma. Note the similarity to Paget’s disease and Bowen’s.
B) The tumor cells stain positive for CK20
Figure 6
Merkel cell carcinoma with squamoid areas.

Figure 7
Microcystic adnexal carcinoma.
A) Note the combination of small keratinizing cysts, solid cords and ductal areas.
B) CK7 stain to show the extent of the tumor.
Microcystic adnexal carcinoma. This carcinoma has a dominant ductal component. These tumors are also known as sclerosing sweat duct carcinoma.
Figure 9

Microcystic adnexal carcinoma. Perineural invasion