Update on Pigmented Lesions of the Sinonasal Tract

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Introduction

Melanocytes are derived from the neural crest and migrate to the skin and mucosa during embryogenesis. They are present in the mucosa of the upper aerodigestive tract in persons of all races. Hyperpigmentation or melanosis of the head and neck mucosa has been reported in the sinonasal mucosa, however, benign pigmented lesions of the sinonasal tract are extremely rare. The most common pigmented lesion of the sinonasal tract is melanoma.

Sinonasal Mucosal Melanoma (SNMM)

The sinonasal mucosa is the most common site of primary mucosal melanoma, even though they account for less than 1% of all melanomas and less than 5% of all sinonasal tract neoplasms. In contrast to cutaneous melanomas that affect younger Caucasian men, patients with SNMM are typically older individuals in the fifth to eighth decade with a peak incidence in the 7th decade. There are no definite etiologic factors, although formaldehyde exposure and smoking have been implicated. No association with radiation, particularly ultraviolet rays, gender or race is known. Although there are some reports of higher incidence in non-white races, these appear to be based on a relative increase in mucosal melanoma in comparison to cutaneous melanoma in the population, and influenced by the significantly lower incidence of the latter in non-white races.

No precursor lesions are known; however, an association with mucosal melanosis is reported. Therefore, it is recommended to biopsy mucosal melanosis before making that diagnosis. SNMM arise *de novo* and rarely, as a metastasis from a cutaneous primary. Patients with SNMM do not seem to be part of dysplastic nevus syndrome or xeroderma pigmentosum kindreds.

Clinical Features

The nasal cavity (including turbinates and septum) is affected most frequently, followed by the paranasal sinuses. Multiple sinuses may be involved by large tumors that extensively involve the skull base. Nasal obstruction and epistaxis are the most common symptoms. Tumors may present with nasal polyps, pain or a nasal discharge of variable duration. Symptoms mimicking ‘sinusitis’ may lead to delay in diagnosis and treatment. Melanorrhea, “coal flecked” or brown nasal discharge has been reported.

Pathology

SNMM are large, bulky and polypoid tumors with a mean size of about 2–3 cm but tumors that involve multiple paranasal sinuses or the skull base may be several cms large. The vast majority of SNMM undergo ulceration and necrosis. The cut surface depends upon the amount of melanin production and may vary from light tan to black.

Microscopically, the tumors may be comprised of epithelioid, spindle, plasmacytoid, rhabdoid, undifferentiated ‘small round blue’ cells and/or multinucleated tumor giant cells (Figs. 1, 2). The tumor cells have high nuclear to cytoplasmic ratio. Epithelioid tumor cells characteristically

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Fig. 1 (A) Epithelioid tumor cells with large, hyperchromatic and pleomorphic nuclei containing prominent, eosinophilic nucleoli. The cytoplasm is amphophilic and opaque. A collar of tumor cells around fibrovascular core (pseudopapillary architecture) is seen. A small amount of melanin pigment is present. (B) Spindle cell SNMM with abundant melanin pigment

have pleomorphic nuclei containing prominent, eosinophilic nucleoli and intranuclear cytoplasmic inclusions. The cytoplasm is usually amphophilic and opaque, often containing melanin pigment (brown to black granules). Mitoses, including atypical forms, are frequently and easily identifiable. Vascular invasion and neurotropism may be identified in up to 40% of cases. A lymphoplasmacytic inflammatory infiltrate admixed with pigment laden histiocytes are commonly identified within or adjacent to the tumor. Large, ulcerated tumors can be extensively necrotic and frequently show a collar of well-preserved tumor cells around blood vessels or pseudopapillary architecture (Fig. 1). Other architectural patterns include solid, alveolar or sarcomatoid. Atypical intraepithelial melanocytes (melanoma in situ) may be noted in the overlying respiratory epithelium and is suggestive of primary SNMM rather than metastatic melanoma (Fig. 3). The tumors usually invade the subepithelial tissue and frequently into the bone, septal cartilage or skeletal muscle. SNMM are similar to the vertical growth phase nodular melanoma of the skin, not otherwise specified.

Immunoprofile

Nearly one third of SNMM may be amelanotic requiring immunohistochemical analysis. Almost all SNMM diffusely express vimentin and S-100 protein. Tumor cells also express melanocytic differentiating markers, e.g. tyrosinase, gp100 (HMB45), melan A and microphthalmia transcription factor (Fig. 2). Epithelial membrane antigen,

Fig. 2 (A) SNMM comprised of undifferentiated 'small round blue' cells resembling non-Hodgkin's lymphoma. Immunohistochemistry with anti-tyrosinase antibody (T311) showing cytoplasmic (B), and anti-microphthalmia transcription factor (mitf) showing nuclear (C) staining reaction

Fig. 3 Atypical intraepithelial melanocytes (melanoma in situ) is present in the respiratory epithelium adjacent to an SNMM. Abundant intracytoplasmic melanin is seen

cytokeratins, neuroendocrine and muscle markers are not expressed.

Differential Diagnosis

SNMM may morphologically masquerade as a variety of benign and malignant neoplasms e.g. ‘small round blue’ cell neoplasms (lymphoma, olfactory neuroblastoma, primitive neuroectodermal tumor, Ewing’s sarcoma, pigmented neuroectodermal tumor of infancy, pituitary adenoma, plasmacytoma, small cell or poorly differentiated neuroendocrine carcinoma, mesenchymal chondrosarcoma), “pleomorphic” neoplasms (sinonasal undifferentiated carcinoma, anaplastic large cell lymphoma, rhabdomyosarcoma, angiosarcoma), or “spindle cell” neoplasms (malignant peripheral nerve sheath tumors, fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, synovial sarcoma). The use of a panel of antibodies against S100 protein, vimentin, and markers of melanocytic, epithelial, neuroendocrine, and lymphoid differentiation is helpful when evaluating undifferentiated sinonasal tract neoplasms. Metastatic melanoma to the sinonasal tract must always be excluded, as the prognosis is significantly different from localized primary SNMM. Metastatic involvement of the head and neck mucosa is usually part of widely disseminated disease, and rarely an isolated event in the course of cutaneous melanoma. Careful clinical history and presence of intraepithelial atypical melanocytes (melanoma in situ) could help differentiate primary from metastatic melanoma.

Table 1 Clinical staging

Stage I	Any size localized tumor without nodal or distant metastases (TxN0M0)
Stage II	Presence of lymph node metastases but no distant metastases (TxN1M0)
Stage III	Presence of distant metastasis (TxNxM1)

Tumor Spread and Staging

At presentation, 70–80% of SNMM are localized, 10–20% have regional lymph nodal and <10% have distant metastasis. During the course of disease, an additional 16–20% may develop nodal metastasis and 40–50% may develop distant metastasis to lungs, brain, bone and/or liver. The most common and prognostically significant staging system in use is given in Table 1. Unlike cutaneous melanomas, the assessment of tumor thickness is greatly compromised due to the lack of a well defined reference point in the respiratory epithelium analogous to the granular layer in epidermis, frequent ulceration, and the generally fragmented and poorly oriented nature of the pathology specimen. Being polypoid, SNMM are in general much thicker (>5 mm) than their cutaneous or oral counterparts, and thickness does not appear to correlate with prognosis.

Genetic Abnormality

Frequent gains of chromosome 1q, 6p, and 8q have been noted along with point mutations in TP53 frequently involving exon 7.

Treatment and Prognosis

Surgical removal with negative margin has the best chance of survival, however, wide free margins of resection are difficult to achieve in the head and neck. Radiation therapy has a palliative role. Local recurrence is frequent (67–92%), may be multiple and is a harbinger of adverse prognosis. Most tumors progress to regional and distant metastasis resulting in poor 5-year disease specific survival ranging from 17 to 47%. Presence of distant metastasis is a poor prognostic factor. Other poor prognostic predictors include advanced age, obstructive symptoms, tumor size (>3 cm), location in paranasal sinuses and nasopharynx, vascular invasion, increased mitoses, undifferentiated ‘small round blue’ cell histology and pseudopapillary architecture (Table 2). Tumor thickness has not been shown to definitively influence survival.

Table 2 Poor prognostic factors

Presence of distant metastasis (Clinical Stage III)
Local recurrence
Large tumor size (>3 cm)
Deep invasion (into muscle, bone or cartilage)
Pseudopapillary architecture
Undifferentiated cells
Vascular invasion
Necrosis
Ulceration

Melanotic (Pigmented) Neuroectodermal Tumor of Infancy (MNETI)

(Synonyms: melanotic progonoma, retinal anlage tumor, melanotic ameloblastoma) This is a rare tumor of infancy comprising of a biphasic primitive neuroblastic and pigmented epithelial tumor cell component. The tumor cells are believed to be derived from the neural crest.

Clinical Features

Most of the patients (>95%) are less than 1 year old. Boys are affected more frequently than girls. The maxillary bone is the commonest site of involvement followed by the mandible, and other craniofacial bones. The tumor presents as a mass in the upper alveolar ridge. The clinical history is of short duration consisting of few weeks to

months (mean 2 months) consistent with the rapid growth of the tumor.

Pathology

The mass is of blue or dark color, with a firm to hard consistency, and a mean size of 3.5 cm. Microscopically, the tumor comprises of a dual population of primitive ‘small round blue’ (neuroblastic) cells and larger, pigmented epithelial cells (Fig. 4). The epithelial cells have abundant cytoplasm and vesicular nuclei. The fibrovascular stroma is densely collagenous accounting for its firm consistency. The two distinctly different types of tumor cells occur in nests that tend to be adjacent to one another. Rarely, neurofibrillary background and rhabdoid differentiation may be seen. There are no or rare necrosis or mitoses.

Immunoprofile and Differential Diagnosis

The melanotic epithelial cells express epithelial and melanocytic differentiation markers, and react with cytokeratins, vimentin and HMB45. The small round blue cells react with CD57 and dopamine-beta-hydroxylase. Neurone specific enolase is expressed in both epithelial and small round blue cells. Interestingly, the tumor cells are negative for chromogranin, S100 protein, neurofilament and desmin. The differential diagnosis includes other

Fig. 4 Melanotic neuroectodermal tumor of infancy. (A, B) Biphenotypic tumor comprising of clusters of ‘small round blue’ (neuroblastic) cells with scant cytoplasm and larger epithelial cells with eosinophilic cytoplasm and intracytoplasmic melanin pigment in densely collagenous stroma. Upon immunohistochemistry, the ‘small round blue’ cells show synaptophysin (C) and the larger, epithelial cells are positive with pan-cytokeratin (AE1:AE3) expression (D) [Images contributed by Dr. Diane Carlson, Memorial Sloan Kettering Cancer Center, New York (copyrights Dr Carlson)]

‘small round blue’ cell tumors, e.g. alveolar rhabdomyosarcoma, non-Hodgkin’s lymphoma, Ewing’s sarcoma/primitive neuroectodermal tumor, neuroblastoma, immature teratoma and melanoma. The characteristic age, location, clinical presentation, histologic and immunohistochemical features should help in diagnosing this rare tumor.

Treatment and Prognosis

MNETI behaves in a benign though locally aggressive and destructive fashion. Complete resection is the treatment of choice. Local recurrences are seen with inadequate excision. Metastases, usually to the regional lymph nodes are well documented, but cannot be predicted by histological features.

Rarely, olfactory neuroblastoma, Ewing’s sarcoma/primitive neuroectodermal tumor and schwannoma occurring in the head and neck may be pigmented. The differentiation would depend on the demonstration of characteristic features of the underlying tumor in spite of the presence of melanin pigment or melanocytic differentiation markers.

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