Introduction

Malignant melanoma is a cancer arising from pigment cells in the skin called melanocytes. Melanoma is a primary skin cancer whose incidence is rising at a faster rate than any other malignancies, except for lung cancer. A recent study from Europe has shown that while the mortality for melanoma stayed relatively stable, the incidence has increased exponentially. The incidence is highest in the countries Australia and New Zealand, followed by North America and Northern Europe. According to the US National Cancer Institute Surveillance Epidemiology and Results database, there is an estimation that 68,130 individuals will be diagnosed with melanoma worldwide in 2010 and that in the US alone, 8700 people will die from melanoma. There are many risk factors associated with the development of cutaneous melanoma. These are generally broken up into environmental and genetic risk factors. Environmental risk factors generally include: an inability to tan, fair complex, blue/green eyes, blonde/red hair, freckling, history of peeling sun burns, immunosuppression, teenage outdoor summer jobs, and a history of tanning booth exposure. Genetic and past medical causes include CDKN2A (p16) mutation, family history of melanoma, history of a prior melanoma, actinic keratoses, non-melanoma skin cancer, xeroderma pigmentosa, atypical nevus, and giant congenital melanocytic nevus. Melanocytes derive from neural crest cells. During embryo genesis, the precursors for melanocytes migrate from the neural crest to the skin, uvea, leptomeninges, and mucous membranes. These are all sites where melanoma can occur. Generally, they remain undifferentiated until they are stimulated where they begin to produce melanin and become melanocytes. Recent studies have looked into the pathways involved in melanoma. Probably, the most important and most researched intracellular signaling pathway is the RAS/RAF/MEK/MAPK pathway. In this pathway, the BRAF protein has been found to be mutated in up to 66% of all melanoma. Also the N-RAS protein is found to be mutated in 15% of melanoma.

There are several histological classifications in melanoma. Superficial spreading melanoma is the most common form of melanoma and arises in a pre-existing nevus. Nodular melanoma is generally regarded as a second most common form of melanoma. Lentigo maligna is an in situ melanoma and is generally a precursor for invasive lentigo malignant melanoma.
Desmoplastic melanoma is a somewhat atypical form of melanoma. 73% are amelanotic, and this often leads to delay in diagnosis. Often this can lead to cranial nerve and skull base involvement. Mucosal melanoma is somewhat different in both its nature and incidence. It is most commonly in the head and neck which presents up to 40-50% of all incidence. However, it is less than 2% of all melanomas. The peak incidence for mucosal melanoma is generally during the 6th and 7th decade. Within the head and neck, the nasal cavity is the most commonly involved site. Generally, the anterior septum is the most likely location followed by the middle and inferior turbinate. The second most common site is the oral cavity, with the hard palate and the maxillary alveolar gingival being the most common subsites. Mucosal melanomas generally do not present with regional spread as only 18.7% will have regional spread at the time of diagnosis. Also ocular melanoma can occur and is usually subdivided into choroidal or conjunctival melanoma.

Staging

Due to the unique nature of melanoma, staging system differs to other head and neck cancers and cutaneous malignancies. Two important classifications one should understand are the Clark and Breslow microstaging systems. The Breslow microstaging system is based on the microscopic depth of invasion of the melanoma in millimeters. The Clark level is based on a one through five level depth of invasion and based on the separate levels of the skin. A Clark level I is confined to the epidermis while Clark level II is a melanoma in both the epidermis and through the basal lamina. Clark level III is a melanoma infiltrating through the papillary dermis while Clark level IV is a melanoma invading the reticular dermis. Clark level V is when the melanoma has infiltrated through the subcutaneous fat. The AJCC revised their staging in 2009 after multivariate analysis of 30,946 patients with stage I, 2, and 3 melanoma and 7,9722 patients with stage IV melanoma. The T staging is based on the thickness of the melanoma. Due to the multivariate analysis showing prognostic differences, ulceration and number of mitoses were added. A T1 tumor is less than 1.0 mm thick. A T2 tumor is 1.01-2.00 mm thick, and a T3 tumor is 2.01-4.00 mm thick. A T4 tumor is greater than 4.00 mm thick. Sub-dividing these further, ulceration will upstage each of these classifications as this is been found to be a poorer prognostic factor. N staging is based on the number of metastatic nodes. N1 classification is one metastatic node, and N2 is 2-3 number of metastatic nodes. N3 disease is 4+ metastatic nodes or nodes that are matted or in transit metastases/solid metastases with metastatic nodes. Microscopic examination is now being used as part of the staging system. M staging is classified based on number of metastases. These are M0, M1a, M1b, or M1c. LDH is used as well in the staging system. An elevated LDH will increase the staging to M1c. The differences most notably from the 6 addition to the seventh addition (2009) of the melanoma staging system include the addition of mitotic rate in T1 melanomas. Also, the immunochemical detection of nodal metastases has not been included for nodal classification. Prior to the latest addition, there was a lower threshold for staging N-positive disease. Classification changes now include all nodal metastases with isolated tumor cells or tumor deposits less than 0.1 mm. This will meet criteria for histologic or immunohistochemical detection of melanoma as N- positive.
Treatment Options

Melanoma is primarily a surgical disease as radiation and chemotherapy have not been found to be sufficient in treatment. Standard approaches include wide local excision, wide local excision with sentinel lymph node biopsy, wide local excision with elective lymphadenectomy, radiation therapy, and/or systemic therapy. Sentinel lymph node biopsy has become more widely accepted as a standard care for patients with melanoma. Multiple studies have shown the efficacy of sentinel lymph node biopsy if identifying occult metastases. This aids in the staging and prognosis of patients.

Lymphatic Drainage

In understanding both malignant melanoma and melanoma of unknown primary, one must understand the lymphatic drainage patterns of the head and neck region and their unpredictability. A study out at M.D. Anderson by Ow et al specifically looked at melanoma and its drainage pathways. They found highly variable drainage pathways but found that the majority of the face, forehead, and cheek drained into the parotid lymph nodes. The parotid gland serves as a major drainage pathway from the face and scalp before draining into the upper jugular nodes. Ow et al also looked at different nodal fields and a number of instances where melanoma drained into multiple lymph node fields. They found that 42% of head and neck melanomas drained into greater than one nodal field. This differed from non-head and neck melanomas which generally drained into one nodal field. Another study out of Croatia sought to examine areas where there was discordance between the primary site and the predicted nodal fields involved. They found that the posterior scalp and upper neck were the most discordant with their projections on drainage. Of the sites examined, the coronal scalp had the highest predictable drainage patterns. Understanding the lymphatic drainage pathways can help focus the search for a primary site in occult disease.

Melanoma of Unknown Primary

Melanoma of unknown primary (MUP) is unique in many accounts which will be discussed in further detail. It was first described in 1952 by Pack et al. Dasgupta first described diagnostic criteria for this unique entity in 1963. MUP generally accounts for 1-8% of all melanomas. It can be divided into 2 clinical groups. These are: metastatic involvement to lymph nodes or non-lymph node disease. There are many theories on the origin of this unique entity. Some theorize it is an unrecognized completely regressed primary melanoma that metastasized prior to regression. Lee et al have speculated that this is the most probable explanation. Other theories include a previous excised undiagnosed melanoma, concurrent and undetected melanoma, a melanoma arising from benign nevus cells found in lymph nodes, or a de-novo malignant transformation. Anbari et al set analyzed their clinical experience with melanoma of unknown primary site. They analyzed 40 patients and found that 22.5% of their patients had a clinically dysplastic nevus prior to developing a MUP. 20% of their patients had a history of regressed skin lesion that was never diagnosed.

Regression in melanoma is well documented with a postulated frequency of 3.7-8.7%. This is thought to be more common in men. Theories on this gender inequality include sun exposure and ignorance for pigmented lesions by men. Some authors believe men will ignore a
lesion for a long enough period to allow for total regression. Melanoma is one of the most common tumors to undergo regression and only 2 other tumors share this characteristic. These are neuroblastoma and hypernephroma. Studies differ on whether regression is found to be a positive or negative prognostic factor. In fact some studies have shown that in primary cutaneous melanoma, regression can be a worse prognosis. There is plenty of experimental data on immunologic studies which support endogenous anti-melanoma immune response. Mauer et al identified circulating factors potentiating lymphocytic cytotoxicity in regressed melanomas. There are also increased lymphocytic infiltrates found in many regressed melanomas. Some studies have shown there is a favorable prognosis associated with the presence of tumor infiltrating lymphocytes and melanoma.

Since 1963, there have been changes to the original diagnostic criteria is set by Dasgupta. Current diagnostic criteria include a metastatic melanoma confirmed clinically, histologically, or immunohistochemically, an absence of a previous cutaneous tumor, pigmented or not, which has been destroyed or excised without histology. There is also an exclusion of unusual primary sites, including areas in the urogenital, otolaryngologic, or ophthalmologic sites. Diagnostic recommendations for evaluation for patient presenting with melanoma of unknown a primary are based on these criteria. Patients should have a review of the previous skin biopsies, a full skin evaluation, CT or MRI imaging of the brain, CT imaging of the chest, abdomen and pelvis, a full ENT examination, and ophthalmologic examination, and a Wood's UV lamp examination. The Woods UV lamp reveals areas of depigmentation or regressed melanomas. This appears to be a fairly strenuous evaluation and has been questioned as being redundant. Tos et al reviewed 103 patients from 1986-2006. 61% of their patients presented with lymph node metastases. Each of their patients underwent a full examination including otoscopy, rhinoscopy, laryngoscopy, ophthalmologic exam, sigmoidoscopy or proctoscopy, and gynecological examination when relevant. Of the 103 patients, only one was found with a possible primary on examination. This patient was thought to have an ocular melanoma; however, this was never proven. The study recommended against multiple special examinations in the workup for metastatic melanoma with unknown primary, but suggested a focused search based on history and physical. PET imaging has also been recently added and the workup for metastatic melanoma with unknown primary. It unfortunately has not been very good at finding unknown primaries as in squamous cell carcinoma. Kole et al study 20 patients of which 8 were melanoma of unknown primary site. None of these patients had a primary site identified after PET imaging. O’neill et al also examined 40 patients diagnosed with a melanoma of unknown primary site, all of which underwent PET imaging. None of these patients had an identification of a primary site. While PET imaging has not been shown to help evaluate for a primary site, it has be useful in O’neill’s study at identifying further metastatic disease. PET imaging is especially limited in the brain and scalp due to high background activity of the brain.

Due to the unique nature of melanoma of unknown primary site, the staging system is slightly different and only takes into account the N and M staging. Melanoma of unknown primary site is classified as stage III or stage IV disease. Any metastatic disease automatically upstages the patient to stage IV. Although theories for the nature of this unique disease cannot be fully explained, it has been shown that this disease has a similar, if not improved, outcome compared to cutaneous melanomas with lymph node metastases. Experts theorize that immune
responses causing regression of the primary tumor incur improved regional and distant control of the disease. With the unusual nature of melanoma of unknown primary site, Pfeil et al sought to determine whether the AJCC 2009 melanoma classification was suitable for melanoma of unknown primary site. They also sought to determine prognostic factors in this patient population. Of the 8897 patients, 172 patients had a melanoma of unknown primary site or a 1.9% incidence. The study, comparing patient based on staging found survival rate significantly different. The survival differences included staging as defined by lymph node metastases, number of satellite or in-transit metastases, the size of satellite/in-transit metastases, the number of regional lymph node metastases, number of distant metastases, the total number of metastases, the M classification at diagnosis, and LDH level at diagnosis. Independent significant prognostic factors in these patients included: age less than 60 years old, stage at diagnosis, the total number of metastases, and the LDH level. Patients with regional metastatic disease had a significantly better overall survival when compared to those with distant metastases. The number of metastatic regional lymph nodes also proved to be a significant factor in multi-variate analysis. An elevated LDH was found to be strongest predictor of unfavorable survival in patients with stage IV disease.

Prognosis

The prognosis of melanoma of unknown primary site appears to be better, or similar, to patients with a cutaneous melanoma with metastases. Katz et al reviewed 19 separate case series from 1952 to 2001. The overall percentage of melanoma of unknown primary site in each study was between 1.2-8.1%. There was also consistent ratio of male greater than female. Of the 19 case series, 7 studies showed a better prognosis. Nine studies showed a similar or better prognosis. Only one study from 1952 showed a worse prognosis. A study from M.D. Anderson performed a Cox regression analysis looking for disease-free survival, disease-specific survival, and overall survival in patients comparing melanoma of unknown primary site with a metastatic melanoma with a known site (MKP). Overall survival was significantly different between the patients with unknown primary site and with melanoma of known primary site. There was a statistically significant difference between male and female patients as well. Also, overall survival was statistically significant for patients with N3 disease. In patients with N1b disease, overall and disease-free survival was better in MKP subjects. However, in each of the other stages patients with melanoma of unknown primary source had both improve disease-free and overall survival. There are many theories on the cause of such improved prognosis. Many theories are based on immune responses to the primary lesion with a likely complete regression. There are also theories based on the melanoma originating from benign melanocytes in lymph nodes. With regards to treating the disease, the surgeon is able to rid the occult primary with a nodal dissection. Pathological studies of lymph nodes have found benign melanocytes in lymph nodes.

Treatment

The treatment options for patients with melanoma of unknown primary site include surgery, radiation, and/or systemic therapy. The mainstay surgery for these patients is a lymphadenectomy or lymph node dissection. Lee et al found improved survival in patients after lymphadenectomy from a nodal metastasis from an unknown primary melanoma. Their research
showed a 5 year survival of 55% in patients after lymph node dissection compared at 27% in patients without lymph node dissection. Their conclusions include most patients with melanoma of unknown primary site can generally expect long-term survival after an adequate lymphadenectomy. They matched patients based on tumor burden and showed improved overall survival in the patients with melanoma of unknown primary site compared to those with cutaneous melanoma. Also, patients with stage IV disease were examined by Lee et al. They found the patients did not have an improved prognosis and M1a disease but otherwise had a significant improvement in overall survival in patients with an unknown primary site versus those with a known primary site.

There's controversy on the use of radiation in patients with melanoma and with a melanoma of unknown primary site. Most believe the melanoma, in general, is not radiosensitive. Ballo et al at M.D. Anderson showed positive data for local and regional control after surgical treatment in patients with melanoma. They found regional control rates of 89% at 5 and 10 years in patients with stage I or stage II melanoma. They concluded that radiation is a useful adjunct especially in patients in whom lymph node dissection or systemic therapies are not options. The suggested indications for adjuvant radiotherapy include evidence of extracapsular spread, multiple lymph nodes, large lymph nodes greater than 3 cm, or recurrent disease. Extracapsular spread incurs a 5% higher regional recurrence rate in patients. Ballo et al found that adjuvant radiotherapy reduced regional recurrence. However, this was not statistically significant. Bastiannet et al performed a systemic review and found that radiotherapy improved locoregional control without improving overall survival. Moncrief et al have suggested that the most important factor preventing locoregional recurrence of melanoma is the primary surgical clearance of the nodal field. Extracapsular spread and large or multiple nodes indicate a higher risk of distant spread and overall mortality. Both appear to remain unaffected by the use of adjuvant radiotherapy. Adjuvant treatments including chemotherapy and systemic therapy have been looked on. Most of these have suggested no improvement in comparing patients with melanoma of unknown primary site with those of a known primary site. As studies continued to look at gene-targeted therapy and melanoma, new drugs are being tested to help in a fight to cure melanoma. Most of these medications are now in either phase I or phase II trials. There is hope then the next several years there will be new adjuvant treatments available for patients with melanoma both of unknown and a known primary site.

Conclusion

Metastatic melanoma of unknown primary site continues to be unique entity in head and neck cancer. Due to its unique presentation and differences with its counterpart, melanoma of unknown primary site should be treated aggressively. A thorough workup is required in the diagnosis of this disease. Surgery is the main treatment option for these patients, and an aggressive surgical approach will yield the best results. Questions continue on whether there is a really improved prognosis compared to cutaneous melanoma with metastases. Most present studies would agree that a melanoma of unknown primary site does incur a better prognosis. There continues to be limited data on adjuvant therapy on patients with a melanoma of unknown primary site. Further studies are currently being done evaluating the role of different genetic markers and protein mutations in melanoma. Melanoma requires a multidisciplinary management team led by the surgeon.
Works Cited


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