Original Research Article

A Study on Malignant Melanoma

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Abstract

Malignant melanoma is malignancy arising from the melanocytes of skin and mucous membrane. Malignant melanoma is most common skin cancer accounting for 78% of skin cancer related deaths. Cho et al., (2005) reported that the risk factors for the melanoma are higher age, male sex, family history of melanoma, higher number of nevi, severe sun burn, light hair color, the data obtained from three large cohort studies. Histopathological classification comprises of 4 subtypes, these are 1. Superficial spreading type, 2. Nodular melanoma, 3. Lentigomaligna melanoma, 4. Acral lentigenous melanoma. Clinical presentation of melanoma depends on location of tumor. Mostly it present as irregular pigmented lesion that grown or changed over time. In our clinical experience we came across different type of melanoma by its site and presentation, which includes melanoma rectum, melanoma sole, melanoma nail bed, melanoma scalp, melanoma foot, melanoma in interdigital area of toes. Melanoma rectum though rare is also entity. Treatment of melanoma varies depending on many factors such as site of presentation, Clark level, and Breslow thickness, having metastasis, and stage of the tumor. Melanoma treatment consists of wide local excision, systemic therapy with ipilimumab, and radiotherapy, intralesional injection of Talimogene, BCG and INF. The clinician should have sound knowledge of various presentations and staging of malignant melanoma and different treatment modalities for each staging. Here we share our experience with malignant.

Keywords

Melanoma, Clark levels, Breslow thickness.

Introduction

Malignant melanoma is malignancy arising from the melanocytes of skin and mucous membrane. Melanocytes originated from neural crest from that they migrate during fetal growth to several organs and tissues, mostly to the skin. Malignant melanoma is most common skin cancer accounting for 78% of skin cancer related deaths (Bradford et al., 2009). The etiology of melanoma varies depending on location of the melanoma. Cho et al., (2005) reported that the risk factors for the melanoma are higher age, male sex, family history of melanoma, higher number of nevi, severe sun burn, light hair color, the data obtained from three large cohort studies (Cho et al., 2005). Whiteman in his case control study reported that number of moles was more strongly related to the development of melanoma in head and neck region (Whiteman et al., 2003). People who are having inherent risk of melanoma and having multiple moles are at high risk for melanoma developing over trunk (Cress et al., 1995). Males are more prone for development of melanoma over trunk, head and neck (Crombie, 1981). Chronic sun exposure is risk factor for the melanoma developing over the head and neck region (Hemminki et al.,
Among the cutaneous melanomas about 30% occur in lower limb, women are more prone for development of melanoma in lower limb, foot and ankle lesions comprise 3-15% of all cutaneous melanomas. Age is more strongly related to the melanoma in head and neck region, reflects over all sun exposure of the head and neck region (Chen et al., 1996). Melanoma over the upper extremity is closely related to the damage due to the sun exposure than family history of melanoma (Zanetti et al., 1992). Hair color also a risk factor for developing melanoma, but it has weak relationship with melanoma over head and neck than other parts of the body (Elwood et al., 1984). The additional risk factors for melanoma are common melanocytic nevi and atypical melanocytic nevi, actinic lentigenes are proved to be markers for cutaneous malignant melanoma. Green et al., (1999) in a case control study of 275 malignant melanoma foot cases studied risk factors for the foot melanoma and found sun exposure is the significant risk factor for the development of melanoma. Interestingly trauma to the foot proposed as a risk factor for the development of the melanoma foot.

Various presentations of melanoma

Here we present some of the cases, one is malignant melanoma rectum is one of the rare presentations it A 37 year old male patient agriculture by occupation presented to the surgical OPD with bleeding per rectum from 6 months and associated with mass per rectum while stool passage from 3 months. On examining the patient pallor present, on per rectal examination a mass felt in right half of the rectum and it is mobile upper border is not reachable, the mass is non tender, fresh blood on glove present after examination. Patient advised to go for endoscopy and TRUS. On endoscopy an eccentric exophytic growth present at anorectum extending up to 6cm and it is blackish in color (Fig. 1). Abdominoperineal resection was performed for this case and specimen sent for histopathology and malignant melanoma was confirmed. On histopathology melanin pigment is seen and on bleaching with potassium permanganate and oxalic acid no color is seen on tumor side of the slide.

Other presented with melanoma sole, A 45 year old female presented with ulceroproliferative growth over the sole of right foot for six months, associated with pain and inability to walk for two months. Patient sustained accidental thorn prick to the right foot eight months back. After one month the blebs and ulcer developed in the thorn prick area and it rapidly progressed to the present ulceroproliferative growth of size 8cm x 6cm (Fig. 2). The growth is associated with the pain and difficulty in walking for two months. Patient noticed blackish discoloration of the growth associated with purulent discharge since then. On examination a single irregular shaped ulceroproliferative growth is seen over plantar aspect on the right foot of size 8cm x 6cm. Blackish discoloration of the lesion is observed. Margins were irregular. It is tender and bleeds on touch. It is associated with purulent discharge.

On lymphnode examination, right inguinal lymphadenopathy is present. On ultrasound inguinal lymphadenopathy is confirmed. Per abdomen examination shows hepatomegaly. Ultrasound and CT abdomen are showing multiple secondaries in liver. Edge biopsy of the growth confirmed malignant melanoma (Figure 8). FNAC of the lymph node demonstrated the metastasis of the melanoma. Below knee amputation was done followed by chemotherapy given to the patient.

Malignant melanoma presented in 45 year old male with pigmented proliferative growth at nail bed of index finger on biopsy malignant melanoma was diagnosed. Here there is
family history and pigmented nevus at the nail bed (Fig. 3).

An ulcerated pigmented lesion presented to the surgical OPD over interdigital area of left foot of 35 year old male patient and on examination left inguinal lymphadenopathy is present. On histopathological examination found that is a malignant melanoma (Fig. 4).

Another case of melanoma presented with ulceroproliferative growth over the scalp in young male of 38 year old (Fig. 5). On histopathology of the growth found that it is a malignant melanoma. In this case there is no family history but sun exposure is the risk factor for this case because the patient is agriculture by occupation, exposed to the sun during field work.

A 50 year old male patient presented with darkly pigmented proliferative growth over the toe from 3months and on edge biopsy of the specimen showed the melanoma features treated with amputation of toe (Fig. 6).

**Results and Discussion**

Malignant melanoma is malignancy arising from the melanocytes of skin and mucous membrane. Melanocytes originated from neural crest from that they migrate during fetal growth to several organs and tissues, mostly to the skin. Malignant melanoma is most common skin cancer accounting for 78% of skin cancer related deaths. The etiology of melanoma varies depending on location of the melanoma. Cho et al., (2005) reported that the risk factors for the melanoma are higher age, male sex, family history of melanoma, higher number of nevi, severe sun burn, light hair color, the data obtained from three large cohort studies. Whiteman et al., (2011) case control study reported that number of moles was more strongly related to the development of melanoma in head and neck region. People who are having inherent risk of melanoma and having multiple moles are at high risk for melanoma developing over trunk. Males are more prone for development of melanoma over trunk, head and neck. Chronic sun exposure is risk factor for the melanoma developing over the head and neck region. Among the cutaneous melanomas about 30% occur in lower limb, women are more prone for melanoma in lower limb, foot and ankle lesions comprise 3–15% of all cutaneous melanomas. Age is more strongly related to the melanoma in head and neck region, reflects over all sun exposure of the head and neck region. Melanoma over the upper extremity is closely related to the damage due to the sun exposure than family history of melanoma. Hair color also a risk factor for developing melanoma, but it has weak relationship with melanoma over head and neck than other parts of the body. The additional risk factors for melanoma are common melanocytic nevi and atypical melanocytic nevi, actinic lentigenes are proved to be markers for cutaneous malignant melanoma. Green et al., (1999) in a case control study of 275 malignant melanoma foot cases studied risk factors for the foot melanoma and found sun exposure is the significant risk factor for the development of melanoma. Interestingly trauma to the foot proposed as a risk factor for the development of the melanoma foot.

**Genetics**

Melanoma in Asians and blacks develop in lower limb and nailbed. Children are at higher risk for atypical melanocytic nevi and melanoma because of germline mutations in the CDKN2A gene coding for the tumor suppressor gene p16 and p19. Among melanoma, familial melanoma account for the 3% to 15% of all malignant melanomas. Melanoma confined to the single generation siblings and malignant melanoma in second
and third degree relatives suggest polygenic inheritance (Tsao, 2000). Other cancers associated with the familial malignant melanoma are mostly pancreatic cancer and breast cancer (Whelan et al., 1995; Borg et al., 2000). Alterations in CDK4 gene, which codes for cyclin dependent kinase4 protein, involved in development of familial malignant melanoma. Germ line mutations in MLH1/MSH2 are involved in familial malignant melanoma (Castiglia et al., 2003). Other genes associated with melanoma are NBS1 XP-genes, CHK2, MC1R, BRCA2.

Melanoma can occur in other parts of the body such as mucous membrane like oral mucosa and rectum and anal canal, ocular melanoma, can occur in gastrointestinal tract etc. Malignant melanoma in rectum is rare malignancy accounting for 1% of all anorectal malignancy. Melanoma rectum is the third most common site for melanoma after skin retina, and it is more common in woman 5th and 6th decade (Ballo et al., 2002; Fratesi et al., 2008). The malignant melanoma in intestine mostly occurs in oropharynx and nasopharynx constitutes about 32.8% and in small intestine constitutes about2.3%. The first case of malignant melanoma was described in 1885 in literature, and high localization was found in maxillary gingival, hard palate, alveolar ridge (Hashemi et al., 2009; Aguas et al., 2009; Lourenco et al., 2009; 2010).

Histopathological classification of melanoma

Comprises of 4 subtypes, these are 1. Superficial spreading type, 2. Nodular melanoma, 3. Lentigomaligna melanoma, 4. Acral lentigenous melanoma.

Superficial spreading melanoma

Large anaplastic melanocytes creeping between the keratinocytes of epidermis in radial growth phase is characteristic of melanoma in superficial spreading type. The pagetoid pattern is seen in the superficial spreading type, in which large melanocytes arranged in nests and creep between the epidermal cells similar to the intraepidermal spread of breast cancer to the nipple. Superficial spreading type most commonly present in lower limb in females and back in males, followed by head and neck and then anterior trunk (Whiteman et al., 2011).

Nodular melanoma

Among malignant melanomas nodular melanoma comprises 10% to 15% melanomas. Age of onset of nodular melanoma is 49years. It is most commonly associated with sun exposure. Usually presents as pigmented nodular lesion. It has poor prognosis. Most common sites for the nodular melanoma are trunk in men and lower limb in women. It has potential to metastisize to distant organs in early stages. It has exclusively vertical growth phase. Microscopically melanoma cells present in the overlying epidermis. The overlying epidermis may be thin or eroded. Cohesive nodule or small nests of tumor cells with expansive growth phase represent dermal component. The cell types are epitheloid cells, spindle sells, mononuclear or multinucleated giant cells (Fernandes et al., 2005; LeBoit et al., 2006).

Lentigo maligna melanoma

Atypical junctional melanocytes are characteristic of lentigomaligna melanoma. Melanocytes arranged side by side along the basal layer. The skin becomes atrophic and in dermis solar elastosis is seen. In papillary dermis lymphocytic infiltration and intense solar elastosis focal fibropalsia is present. Lentigo maligna melanoma often spreads to the adnexal structures (Barnhill, 2004).
Acral lentigenous melanoma

Histologically this melanoma characterized by, in radial growth phase there is marked acanthosis and hyper keratosis, elongation of intercapillary crests and proliferation of atypical melanocytes along the basal layer of epidermis at the periphery of the tumor. Large atypical melanocytes with large nuclei and nucleoli, often bizarre cytoplasm, containing large amount of cytoplasm represents intradermal component. In vertical growth phase, tumor nodules contain predominantly spindle cells and are associated with desmoplastic reaction. The junctional component of thicker tumors shows formation of nests and migration of anaplastic melanocytes toward the stratum corneum.

Clark level

Level I: melanoma cells present only in epidermis and adnexal epithelium featuring a melanoma insitu.

Level II: melanoma cells invade papillary dermis with only few cells present in junction between papillary and reticular derrmis

Level III: melanocytes fills the papillary dermis and to the superficial vascular plexus without invading reticular derrmis

Level IV: melanoma invasive and invade the reticular derrmis

Level V: cancer invades hypodermis

Breslow thickness

Thickness of the tumor is represented by the breslow thickness in millimeter. It is divided into <1mm to >4mm : <1mm thickness, 1.01mm to 2mm thickness, 2.01mm to 4mm thickness, >4mm thickness

Management of melanoma

Clinical presentation of melanoma depends on location of tumor. Mostly it presents as irregular pigmented lesion that grown or changed over time. In our clinical experience we came across different types of melanomas. Other presentations vary according to the location of the tumor. Investigation of the tumor is mainly by biopsy. The choice of incisional biopsy and excisional biopsy is depending on the size of the tumor and margin availability. Incisional biopsy should be done under local anaesthesia. Excisional biopsy is done with margin.

Treatment of melanoma depends on stage of the tumor, for stage 1 treatment of melanoma is wide local excision with adequate margin. The margin with which wide local excision is done is depends on the tumor thickness. For melanoma in situ the margin is 0.5 to 1cm and less than 1cm is 1cm margin, for 1 to 2cm is 1 to 2 cm for more than 2cm, 2cm is the margin. It can be modified as per the location and anatomical feasibility. Based on workup and clinical staging patients are stratified into 6 groups.

Staging of melanoma

Stage 0: melanoma in situ; stage IA and IB with thickness 0.75mm or less, regardless of ulceration and mitotic rate.

Stage IA: with thickness 0.76 to 1mm with no ulceration and mitotic rate 0 per mm$^2$.

Stage IB: with thickness 0.76 to 1mm with ulceration or mitotic rate greater than or equals to 1 per mm$^2$.

Stage II: thickness 1mm with nay feature like ulceration and mitotic rate and clinically negative nodes
Stage III: clinically detected positive nodes. Microscopic satellitosis and or in transit disease.

Stage IV: is metastatic disease.

Treatment of melanoma according to NCCN guidelines, in stage IA and IB is with wide local excision with adequate margin sentinel lymphnode biopsy needed for stage IB and II. Stage III with sentinel lymphnode biopsy positive wide local excision of the primary tumor and complete lymphnode desecion and adjuvant therapy with interferon alfa or high dose ipilimumab. For clinically positive for lymphnode complete therapeutic lymphnode dissection along with wide local excision of the primary, adjuvant therapy is also considered with radiotherapy and interferon alfa and ipilimumab. Intraliesional injection option for melanoma is Talimogene laherparepvec (T-VEC), BCG, IFN, IL-2. Topical application of imiquimod for superficial dermal lesions is considered. And consider radiotherapy for unresectable tumors of stage III clinical satellite lesions. Isolated limb perfusion or infusion is the treatment option for stage III with clinically satellite lesion.

**Fig.1** Melanoma presenting as bleeding mass per rectum

![Fig.1](image1)

**Fig.2** Melanoma sole presented with ulceroproliferative growth over sole

![Fig.2](image2)

**Fig.3** Melanoma toe

![Fig.3](image3)
**Fig. 4** Melanoma in interdigital area

![Image of Melanoma in interdigital area]

**Fig. 5** Melanoma over the scalp

![Image of Melanoma over the scalp]

**Fig. 6** Melanoma over heel

![Image of Melanoma over heel]

**Fig. 7** Melanoma of nail bed

![Image of Melanoma of nail bed]
Prognostic factors of melanoma

The prognostic factors were analysed and demonstrated in various studies. The most important prognostic factor for melanoma is stage of the disease. The staging of the malignant melanoma is depending on the breslow thickness. Other factors includes ulceration, presence of metastasis and site of metastasis is also a predictor of survival and have prognostic significance, number of metastatic nodes and tumor burden are predictor of survival in patients with nodal metastasis. The measured tumor thickness is most important prognostic factor for melanoma (Balch et al., 1978). The tumor thickness reflects more accurate prognosis of the melanoma than tumor invasion. Ulceration in melanoma indicates absence of epidermis over the tumor, indicating the more mitotic rate of tumor in the melanoma. This factor is associated with increased metastatic behavior of the tumor. Ulcerated melanomas without nodal metastasis is having worse prognosis than stages of melanoma with nodal metastasis (Austin et al., 1994). Age is the independent prognostic factor for melanoma, older people are having thicker melanomas and ulcerations are poor prognostic outcome for the melanoma in elder ages (Averbook et al., 1998; Sahin et al., 1997). Melanoma having metastasis to the lung is the only one having better prognosis than melanoma spreading to other organs.

In conclusion, the malignant melanoma is one of the most common cutaneous malignancy. It is presented in various forms in body. The clinician should have sound knowledge of various presentations and staging of malignant melanoma and different treatment modalities for each staging. Here we share our experience with malignant melanoma.
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