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Challenges in Diagnosis of Melanoma from the Perspective of a Pathologist

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ABSTRACT

Introduction: Melanoma is an aggressive melanocytic neoplasm with a continuously increasing incidence worldwide. Vast majority of melanoma arises from skin whereas a small subset of melanoma can arise as a primary malignancy of mucosal membranes. Gastrointestinal (GI) melanoma is usually metastatic in origin whereas primary GI melanomas are extremely rare. Anorectal Melanoma comprises of 1/% of all malignant neoplasms of this area. About 70% of these lesions are pigmented whereas 30% of them are amelanotic. Upto 25% of the patients with melanoma develops recurrent disease locally or in regional lymph nodes.

Materials And Methods: This is a prospective study conducted in a tertiary care hospital comprising of six cases of Melanoma. We studied the cases according to their age, sex, clinical presentation, site, radiological findings, histopathological findings, immunohistochemical findings and treatment provided.

Results: This study comprises of six cases of Melanoma among which five cases are primary one case is recurrent. Among the five primary cases, four cases have GI origin (sigmoid colon, rectum, anal canal) one case originated from skin involving left foot. There is a single case of recurrent MM involving right inguinal lymph nodes with a history of primary MM in the right lower limb. The patients belong to the age group of 6^{th} to 8^{th} decade with male preponderance. Histopathological examination of formalin fixed paraffin tissue sections was done followed by Hematoxylin & Eosin and Immunohistochemical staining which confirmed the diagnosis of Melanoma.

Conclusion: Melanoma is an aggressive melanocytic neoplasm that carries a poor prognosis. It commonly involves skin. Its occurrence in GI tract is rare in which primary lesions are exceedingly unusual. Diagnosis and Treatment require multidisciplinary team approach with surgery remaining as a cornerstone of treatment.

KEYWORDS: Abdomino-perineal resection, colonoscopy, hemicolectomy, histopathological examination, immunohistochemistry, melanocytes, melanoma, wide local excision

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INTRODUCTION

Melanoma is an aggressive melanocytic neoplasm with a continuously increasing incidence worldwide. It is associated with increased rate of mortality and morbidity and is responsible for more than 80% of all deaths from skin cancer. It originates from transformed melanocytes and can involve cutaneous or non-cutaneous regions like eye, paranasal sinuses, oral mucosa or urinary tract [1].

Gastrointestinal (GI) melanoma is commonly metastatic in nature[2] , primary GI melanomas are very rare and constitutes only 2% of all mucosal melanomas [3], involves pharynx (32.8%), anal canal (31.4%), rectum (22.2%), oesophagus (5.9%), stomach (2.7%), small bowel (2.3%), gall bladder (1.4%) and colon (0.9%)[4].

Primary colonic melanoma is an extremely rare diagnosis which most commonly involves ascending colon

(46.7%) and caecum (26.7%)[2]. Anorectal MM constitutes 1% of all malignant neoplasms of anorectal region and only 0.3-1% of all Melanoma[5]. These lesions may be polypoidal or sessile. About 70% of anorectal melanomas are pigmented, while 30% are amelanotic. Immunohistochemistry (IHC) is required for confirming the diagnosis of amelanotic melanoma[6]. The diagnosis is often confused with hemorrhoids as the most common clinical feature is bleeding per rectum. More common in females of 5th to 6th decade . Majority of patients present with locally advanced or metastatic disease[7]. The most common cause of death is metastasis[8]. Surgical management of patients with anorectal melanoma is debatable[9]. Abdominoperineal resection (APR) is usually done in case of large tumors where wide local excision (WLE) can not be done[10,11]. Chemotherapy, radiotherapy , immunotherapy is considered only to influence overall survival[11].

Involvement of lower extremity by Melanoma is more common in caucasian females, where it involves foot and toes very rarely. Such an involvement is attributed to a number of factors like ultraviolet light exposure , sun sensitivity, multiple benign or atypical nevi, immunosuppression. The melanoma of foot has got worse prognosis[12,13,14]. Prognosis of metastatic melanoma is worse than primary melanoma[15].

Local recurrence rate of Melanoma is about 3.8%. It occur locally or in regional lymph nodes[16,]. Locoregional recurrence refers to recurrence occurring locally at the site of primary lesion, regionally in the draining lymph nodes and/or anywhere in between, but do not include distant metastasis. It can either be true recurrence following adequate excision or persistent disease due to insufficient excision[16]. The local recurrence rate is 2 to 3% while the risk factors which increases the rate of local recurrence include increased primary lesion thickness and ulceration[16]. Surgical resection is the mainstay treatment for locoregional recurrence and it provides best chance of long term cure. Prognosis with local metastasis is controversial [17].

MATERIALS AND METHODS

This is a prospective study conducted in a tertiary care hospital comprising of six cases. All patients presenting with specific clinical features depending on the location of Melanoma were included in the study. Out of all lesions, 5 were primary and one was a case of recurrent disease involving regional lymph node after surgical removal of the primary lesion. The anatomical locations of the lesions taken into consideration were-colon, rectum, anal canal, foot for primary lesion, inguinal lymph node for recurrent disease. Histopathological and immunohistochemical analysis was performed on formalin fixed paraffin-embedded samples. The biomarkers tested in our tumor samples were HMB-45, Melan-A, Vimentin and S100 for confirming the diagnosis of Melanoma. We studied the cases according to their age, sex, clinical presentation, site, radiological findings, histopathological (HP) findings, IHC findings and treatment provided. Informed consents were taken from all the patients.

RESULTS

CASE 1: Primary Melanoma of sigmoid colon

A 60-year-old male presented with 8 months history of symptoms comprising of abdominal cramping, bloating and abdominal pain. He also complained of intermittent constipation since the same duration and 3 episodes of hematochezia 2 days prior to admission. His medical and surgical history was unremarkable with an exception of 30 pack per year smoking history.

Contrast enhanced (CE) CT scan abdomen revealed a mass within the sigmoid colon with luminal narrowing. He underwent left hemicolectomy and the specimen was sent in the department of Pathology for Histopathology (HP) examination. The gross size of the tumor was 10x6x4cms, 5 lymph nodes were identified. HP examination revealed presence of lesion consisting of dense infiltrate of cells with large pleomorphic nuclei with prominent nucleoli and presence of abundant intracellular and extracellular coarse non refractile brown pigments, indicating melanin (Fig.1). On IHC, the lesions showed positive expression of Melan-A (Fig.2), Human Melanoma Black 45 (HMB-45) (Fig.3) and Vimentin (Fig.4), which confirmed the diagnosis of Melanoma. All 5 lymph nodes showed reactive lymphoid hyperplasia. To exclude metastatic lesions from primary cutaneous or ocular melanoma, a thorough dermatological and ophthalmic examination was performed which revealed no suspicious skin or ocular lesions. Whole body CT scan did not show any other lesion apart from sigmoid colon mass.
The patient refused any adjuvant therapy and was discharged 10 days after surgery. Regular out patients follow up was done for 1 year which revealed no recurrence.

CASE 2: Primary Melanoma of rectum

A 57-year-old-male presented with one year long history of alternating constipation and diarrhea and associated painless rectal bleeding since last 1.5 months. The bleeding was fresh and admixed with stool. On laboratory examination the hemoglobin level was within normal limits (14.5g/dl). CECT whole abdomen revealed enhancing broad based polypoidal lesion measuring 4.5x4.3cms in the lower rectum with luminal narrowing with no evidence of enlarged mesorectal nodes. Final diagnosis of Polyp was given.

Per rectal examination revealed normal anal resting and squeeze tone and large mass felt on finger. Colonoscopy was perfomed that showed 5x4cm ulcero-proliferative lesion 6 cm away from the anal verge, surface showing ulcers with irregular margins, base covered with clotted blood and exudates. Biopsy was taken during colonoscopy and sent for HP examination. We received 4 bits of greyish-black tissue fragments altogether measuring 0.8cc. The biopsied tissue was processed and stained with hematoxylin and eosin (H&E) stain. Microscopical examination demonstrated sheets

of large pleomorphic polygonal cells with nuclear hyperchromasia, prominent nucleoli. Abundant intracellular and extracellular coarse non refractile brown pigments seen indicating melanin (Fig.5 & Fig.6). The diagnosis of Melanoma was confirmed taking into account of CECT findings of polypoidal lesion (Fig.7). To exclude the possibility of metastatic melanoma, the patient was re-examined for any skin lesions and no skin lesions were found. Whole body CT scan did not detect any other lesion.

The patient underwent APR and the speciment was sent for HP examination. We found one blackish ulcerated polypoid mass measuring 4cmx4cmx3cm in the lower part of the rectum. HP examination was done which revealed the diagnosis of Melanoma infiltrating into the muscle layer reaching upto the serosa. No lymph nodes were identified in the specimen. Human Melanoma Black 45 (HMB 45) IHC was done that showed diffuse and strong positivity in the neoplastic cells, that confirmed the diagnosis of Melanoma. The patient was followed up for 6 months . He was in good health during the follow up period.

CASE 3: Primary Melanoma of Anal canal

A 70-year-old-man presented with 6 months history of painful rectal bleeding, tenesmus and 5 kg weight loss. Per rectal examination revealed a hard mass located just above the anal verge. A biopsy was taken from the mass which suggested Melanoma. To exclude the possibility of metastatic Melanoma, the patient was re-examined for any skin or ocular lesion, but no lesion was found. CE-CT abdomen and pelvis revealed heterogeneously enhanced circumferential wall thickening of lower rectum and anal canal extending upto the anal verge. MRI pelvis revealed irregular T2 hypo to hyperintense circumferential wall thickening with diffuse restriction involving rectum and anorectal junction extending upto the anal verge, indicating possibility of neoplastic etiology. Whole body CT scan could not detect any other lesion. APR was done with end colostomy. The specimen revealed an ulcero-proliferative circumferential tumor measuring 6x4x3cms involving the dentate line and below. Microscopical examination showed Melanoma that was confirmed by HMB-45 IHC examination which showed diffuse and strong positivity in the neoplastic cells (Fig.8 & FIG.9). MRI pelvis (Fig.10) was also contributory. Ten lymph nodes isolated from peri-rectal fat out of which 4 showed metastatic deposit of the same tumor. The patient was sent for radiotherapy, but he denied further treatment. After Six months he came for follow up and agreed to take further treatment.

CASE 4: Primary Anorectal Amelanotic Melanoma

A 73-year-old female patient presented with chief complaints of bleeding per rectum, increasing constipation and associated with prolapsing mass per rectum since 9 months. She was hemodynamically stable. Clinical history and examination findings led to a provisional diagnosis of hemorrhoids. The mass was excised and sent to our department as specimen of thrombosed hemorrhoids. We received a single globular greyish-brown soft tissue piece measuring 5x4x3cm with surface congestion (Fig.11). The tissue was processed and stained with H&E stain. Microscopic examination revealed spindle to ovoid pleomorphic tumor cells with hyperchromatic to vesicular nuclei, prominent eosinophilic nucleoli, and moderate to abundant eosinophilic cytoplasm, arranged in sheets with intersecting fascicles with focal alveolar pattern. Large number of atypical mitotic figures seen along with areas of necrosis and presence of few bizarre binucleated and multinucleated cells. (Fig.12). Based on the histological findings a differential diagnosis of amelanotic melanoma, undifferentiated carcinoma, gastrointestinal stromal tumor (GIST), non-hodgkin lymphoma (NHL) was made. A panel of IHC markers was advised for definite diagnosis, which included HMB-45, S100, CK (cytokeratin) , CD117 and LCA (leucocyte common antigen). The tumor cells showed positive expression of HMB-45, S100, whereas other markers were negative. Hence, a diagnosis of anorectal amelanotic melanoma was confirmed based on IHC findings. The patient had symptomatic improvement and was referred to radiation/medical oncology department for adjuvant therapy. Six months have passed. She did not have any complaints on follow up.

CASE 5: Cutaneous Melanoma of left foot

A 58-year-old female patient presented with clinical history of bruise involving the skin overlying the 4^{th} toe and junction between the 4^{th} toe and 3^{rd} toe of left foot. The patient did not pay much attention to it initially unless it progressed to a painful irregular discoloured ulceration involving the dorsal and planter surfaces of 3^{rd} and 4^{th} toe, planter surface of 5^{th} toe as well as extending into the sole (Fig.13). The patient was a known diabetic and had a family history of melanoma of her paternal uncle. She underwent amputation of the 4^{th} toe and wide local excision of the rest of the lesion with 3 cm margin. HP examination revealed multiple single and nested atypical melanocytes with varying shape and size which extended along the dermo-epidermal junction. Multiple pagetoid single and nested dysplastic melanocytes were seen within all levels of epidermis and dermis with irregularly distributed melanin pigment, accompanied with epidermal hyperplasia, elongation of rete ridges. HP findings suggested the diagnosis of Melanoma which was confirmed by HMB-45 IHC. The atypical melanocytes showed positive expression of HMB-45 (Fig.14). Ater six months when she came for follow up no recurrence was noted.

CASE 6: Recurrent Melanoma involving right sided inguinal lymph nodes

A 53-year-old man presented with isolated regional lymph node recurrence (RLNR) involving right sided inguinal lymph nodes 12 months after WLE of the primary

tumor involving right lower limb.The greatest size of the involved lymph node is 6cm in diameter (Fig.15). There was presence of ulceration in the primary lesion and he had prior negative sentinel lymph node biopsy (SLNB). Excision and dissection of all regional lymph nodes were done and the patient underwent adjuvant chemotherapy. The excision of the lymh ode mass was done and we received 8 soft tissue pieces measuring one cc which were fixed in 10% neutral buffered formalin, entirely processed and stained with H&E stain. HP examination revealed 12 lymph nodes out of which 2 lymph nodes showed metastatic deposit of Melanoma. The diagnosis was confirmed by IHC. The metastatic deposits of Melanoma in the respective lymph nodes showed positive expression of HMB-45(Fig.16).

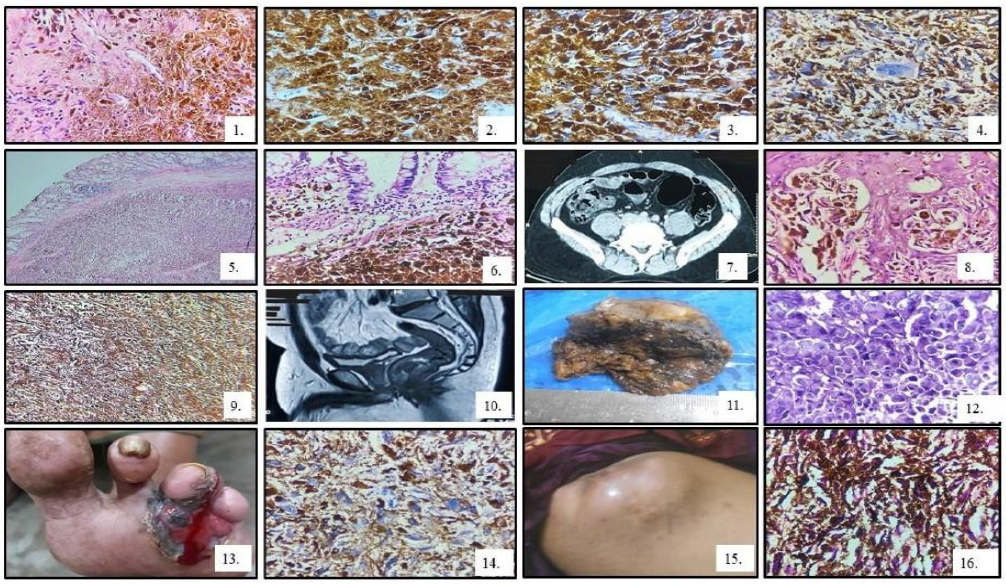

Fig. 1: Diffuse infiltrate of pleomorphic cells with abundant intracellular and extracellular melanin pigment deposition in sigmoid colon malignant melanoma (400X).
Fig. 2: Positive expression of Melan-A in the neoplastic cells in sigmoid colon malignant melanoma (400X) on IHC.
Fig. 3: Positive expression of HMB-45 in the neoplastic cells in sigmoid colon malignant melanoma (400X) on IHC.
Fig. 4: Positive expression of Vimentin in the neoplastic cells in sigmoid colon malignant melanoma (400X) on IHC.
Fig. 5: Low power (100X) view of Rectal malignant melanoma on histopathological examination (HPE).
Fig. 6: High power (400X) view of Rectal malignant melanoma on histopathological examination (HPE).
Fig. 7: CE-CT whole abdomen showing enhancing broad based polypoidal lesion in the lower rectum with luminal narrowing in Rectal malignant melanoma.
Fig. 8: High power (400X) view of Anal canal malignant melanoma on histopathological examination (HPE).
Fig. 9: Positive expression of HMB-45 in the neoplastic cells in Anal canal malignant melanoma (400X) on IHC.
Fig. 10: MRI pelvis showing T2 hypo to hyperintense circumferential wall thickening with diffuse restriction involving rectum and anorectal junction extending upto the anal verge in anal canal malignant melanoma.
Fig. 11: Gross image of anorectal amelanotic melanoma mistaken as hemorrhoid clinically.
Fig. 12: HPE (400X) showing spindle to ovoid pleomorphic tumor cells with hyperchromatic to vesicular nuclei, prominent eosinophilic nucleoli, moderate to abundant eosinophilic cytoplasm, arranged in sheets in anorectal amelanotic melanoma.
Fig. 13: Gross image of cutaneous malignant melanoma involving toes extending to the sole of left foot.
Fig. 14: Positive expression of HMB-45 in the neoplastic cells in cutaneous malignant melanoma of left foot (400X) on IHC.
Fig. 15: Image showing enlarged lymph nodes of right sided inguinal region.
Fig. 16: Positive expression of HMB-45 in the neoplastic cells of metastatic deposits of cutaneous malignant melanoma of right foot in right sided inguinal lymph nodes (400X) on IHC.

DISCUSSION

Primary melanoma of colon is a very rare entity with the pathogenesis being tumor regression and ectodermal differentiation theories. The average age of patients is around 60 years without gender predilection [2]. Our patient with primary colon melanoma as 60 year of age. The diagnosis is sometimes difficult by H&E staining. Subsequently it is confirmed by specific IHC staining. S100 being highly sensitive (90%) and HMB-45 positivity has 100% specificity and 80% sensitivity [2,18]. Our case showed positive expression of HMB-45, Melan-A and Vimentin. As GI melanomas are mostly metastatic in origin, a thorough physical and radiological examination are required to exclude metastatic lesions from primary cutaneous or ocular melanomas, as done in our case. Therefore, when there is no history of previous melanoma, a whole body dermatological and ocular examination is critical along with whole body CT or MRI. These investigations were done in our series also. In case of local disease, surgical resection with wide margins is gold standard, however, surgery also provides palliative advantage in patients with symptomatic melanoma [2]. Ulceration and thickness of the tumor are important predictive factors for the prognosis of this tumor[19,20]. The prognosis is determined by depth of invasion and disease

stage. Metastatic colon melanomas have a 5 year survival of 33%, while primary colonic melanomas seem to have a better prognosis [21,22].

Our patient had sigmoid colon melanoma for which he underwent left hemicolectomy.

Melanoma of rectum is also rare and reported in older patients. The clinical presentation includes rectal bleeding with or without pain, as seen in our case. Surgery is the main treatment which varies from WLE to APR. However, the relative benefits of these individual procedures is controversial as prognosis is same in both cases[9,23]. In our case APR was done.

Primary anorectal melanoma is very uncommon but aggressive tumor, only a few cases have been reported in the literature, therefore, it is difficult to draw conclusion regarding optimal treatment and outcome[24,25]. Treatment modalities include WLE, APR, in our case APR was done with end colostomy. Adjuvant radiotherapy is well tolerated and improves loco-regional control[26]. Our patient was also sent for adjuvant radiotherapy, but he denied additional treatment.

Anorectal amelanotic melanoma is an extremely rare entity[27]. Rectal bleeding is the most common clinical presentation. It is more common in females. Hemorrhoids, polyps and other malignancies are usual differential diagnoses[9,28]. Digital rectal examination reveals a hemorrhoid like mass in the anorectal junction, and grossly it is often misdiagnosed as hemorrhoid. As amelanotic melanoma has absent or very few melanin granules, it is difficult to differentiate it from various other anorectal tumors such as adenocarcinoma, squamous cell carcinoma, GIST and lymphoma. Therefore, immunostainin is required for confirmation[27]. In our series amelanotic melanoma presented with complaints of rectal bleeding and as coming down of a mass er rectum. Initially it was diagnosed as hemorrhoid. But after histopathology the diagnosis of amelanotic melanoma was done. The Surgery is the optimal treatment, considered as palliative, without any significant improvement in the overall survival. The role of adjuvant chemotherapy has not been established, however immunotherapy has improved the prognosis of this highly fatal malignancy[28,29].

Among cutaneous Melanoma, more cases of acral melanoma have been recorded compared to non acral melanoma among Asian population[30-32]. Bradford et al. found that 62.8 year was the mean age for diagnosis of acral melanoma whereas 58.5 year for non acral melanoma. Acral melanoma is more frequent in females and in lower extrimity[33,34]. We had a case of 58-year-old female presenting with acral melanoma involving toes of left foot extending to the sole. Surgical management is either WLE or amputation for acral melanoma. For patients with advanced local lesion, amputation helps in local control and and may prove to be curative[33,34]. Our patient underwent amputation of the involved toe and WLE with 3cm margin.

SLNB for cutaneous melanoma is steadily gaining compliance as a standard of care[35,36]. It has been found that in several series with progressively increasing follow up duration, the overall rate of recurrence for patients with a negative sentinel lymph node (SLN) is persistently found to be between 9% to 14%[37-38]. In our case also, the patient had prior negative SLNB findings but developed RLNR after 12 months of surgical management of the primary tumor. For recurrent disease confined to the regional lymph nodes, completion lymphadenectomy provides potentially curative treatment. For recurrence involving inguinal lymph nodes, inguino-femoral, iliac and obturator, pelvic lymph node dissection is recommended [39]. Adjuvant radiotherapy when used to in conjunction with complete lymph node dissection, may improve locoregional control and demonstrate reduction in regional recurrence rates following lymph node dissection in groin , neck, axilla[40,41,42].

CONCLUSION

Melanoma is an aggressive melanocytic neoplasm that carries poor prognosis. It commonly involves skin. Occurrence of Melanoma in GI tract is rare, in which primary lesions are exceedingly unusual. The histopathological diagnosis needs IHC in addition to routine H&E staining along with clinical and radiological correlation. Treatment requires multidisciplinary team approach with surgery remaining as the cornerstone of treatment. The role of adjuvant therapies is minimal but may improve locoregional control and demonstrate reduction in regional recurrence rate. Isolated RLNR occurs mostly within 1-2 years after diagnosis of primary Melanoma. SLN status is an important prognostic factor in these tumors.

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