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MERKEL CELL CARCINOMA OF SKIN: THE MISSING LINK

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ABSTRACT

MCC is subtle as a considerable driving mechanisms of this cancer are entrenched which is still ineffectively comprehended process, for example, immune surveillance, epigenetic changes, atypical protein expression, posttranslational alterations and microRNAs. Going ahead, utilization of functional genomics and proteomics is incredibly needed to give the bits of knowledge important to develop effective treatments. A number of the oncologic pathways seen in different cancer have been thoroughly assessed for missense and nonsense mutations in MCC with inadequately low yield. It is conceivable that we have simply been taking a gander at the wrong pathways, and characterized mutations are holding up to be investigated. Despite the fact that the particular cell of origin is still discussed, tumor cells show confirmation of neuroendocrine differentiation by both immuno-histochemical study and electron microscopy. Various chromosomal variations have been found; the most incessant are a distal deletion including 1p35-36 and loss at 13q14.3. Wide local excision, with lymph node dissection and adjuvant radiation treatment, is the most well-known technique for treatment. Chemotherapy has delivered little advantage in general survival, albeit metastatic tumors have shown chemo sensitivity. General survival rates have fluctuated. On the off chance that if metastasis is found, then death will occur within a months of its detection. Though, patients with stage I tumors have been accounted with survival rates as high as 83%. This underscores the requirement for a high record of suspicion for the tumor, expeditious and precise diagnosis, and early remedial intercession.

KEYWORDS: carcinogenesis, neuroendocrine carcinoma of the skin, Merkel cell, Chemotherapy, Radiation therapy, Signaling pathway.

INTRODUCTION

Merkel cell carcinoma (MCC) is an exceptionally aggressive carcinoma of the skin.[1-2] In 1972, Toker depicted five patients with irregular skin tumors where histologically anastomosing trabeculae and cell nests in the dermis were found, so he utilized the name 'trabecular carcinoma of the skin' .Then, the disclosure of electron-dense neurosecretory granules in the tumor cells allowed their classification among the neuroendocrine carcinomas. As Merkel cells, which belongs to the amine precursor uptake and decarboxylation framework (APUD) framework, are the main cutaneous cells that shape such granules, it was proposed that these carcinomas have derived from these cells.[3] Prominently, recent evidence demonstrates that Merkel cells are derived from pluripotent epidermal stem cells. The American Cancer society anticipated for 2014, 2500 new instances of MCC in the USA alone; the frequency of MCC would hence surpass that of cutaneous T-cell lymphomas (Figure: 1). within a 15-year period from 2000 to 2015, the MCC cases have rose with a factually significant yearly increment of 8%. This ascent is more sensational than the expanded rate of cutaneous melanoma.[4] Despite the fact that the rate of melanoma, which is principally because of the higher number of melanomas analyzed early, has risen radically in last 15 years i.e 2000 and 2015 was just 3% every year.[5]

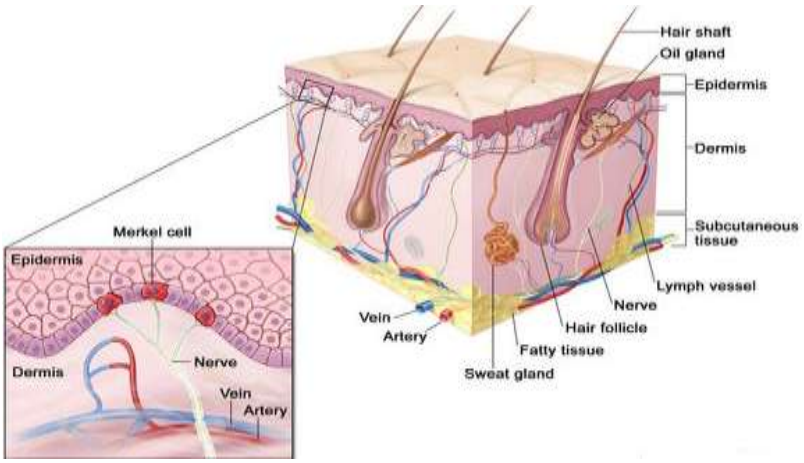

Figure:1 Merkel cell carcinoma of skin

Besides, the death rate of MCC is 35% which is definitively higher than that of melanoma. MCC is an old age carcinoma; the mean age of subjects for initial diagnosis is 70 years. MCC subjects are frequently immunosuppressed.[6] For instance, MCC happens considerably more frequently in subjects with organ transplants and HIV infection. There is a high level of relationship of MCC with squamous cell carcinoma, basal cell carcinoma, Bowen disease, inner malignancies and hematological neoplasias.[7-9] The role of UV light in the development

of MCC is considered to be immunosuppressive than as a mutagenic/carcinogenic impact. Pathogenetically, notwithstanding aggravated antigen presentation, the prompting of immunosuppressive cytokines, for example, interleukin (IL) - 10 and tumor necrosis factor a (TNF-a), the isomerization of trans-urocanic acid to cis-urocanic acid and the formation of reactive oxygen species are faulted.[10]

Mutational Analysis in MCC

MCC reaction to treatment modalities and forecast prognosis is capricious, and clinical and histologic attributes have constrained utility to foresee result.[11-13] Underlying the confounding common history of MCC have unique contrasts in chromosomal variations, genetic transformations, expression profiles and epigenetic controls of individual tumors are still ineffectively understood. Recently, Merkel cell polyomavirus (MCPyV) has been discovered in up to 80% of MCCs. Better comprehension of MCC at the molecular level will give much required knowledge with respect to diagnosis, prediction of reaction to aggressive surgical excision and chemo-radiation, and the development of targeted treatment.[14]

Chromosomal Abnormalities

Chromosomal deviations can conceivably give bits of knowledge into the pathogenesis of MCC, uncover particular gene targets, and serve as a diagnostic asset.[15] Initial invasions into chromosomal investigation in MCC used comparative genomic hybridization (CGH) to characterize copy number variations, however did not have the resolution to segregate particular gene candidates. Commonly amplified regions have been studied on chromosomes 1, 5, 6, 8 and 20, and incessant loss on chromosomes 13 and 4. Chromosomal modifications are connected with larger tumors at higher risk for metastatic spread.[16-17] Nonetheless, most investigation need proof for high level amplification. The appearance of microarrays has incredibly enhanced the resolution of hybridization, and can give copy number variations data at the single gene level. Utilizing array CGH technology, Paulson et al. assessed 23 MCC specimens, and comparatively found that tumors frequently carry extra duplicate copy of chromosomes 1, 3q, 5p, and 6 and lost chromosomes 3p, 4, 5q, 7, 10 and 1. MCPyV positive tumors had less genetic variation.[18] Three chromosomal region, including a deletion of 5q12–21 found in 26% of tumors, a deletion of 13q14–21 additionally found in 26% of tumors that contains the RB1 tumor silencer, and amplification at 1p34 present in 39%, which contains the L-Myc (MYCL1) oncogene.[19]

Abnormal Signaling Pathways in Tumor Cells

Cytotoxic Activity by chemotherapy has been the backbone in the administration of advanced MCC. Nonetheless, it neglected to exhibit enhanced survival and is connected with a high death rate. Up to this point, aberrations in sign transduction adding to the oncogenic phenotype of MCC were to a great extent obscure. In-depth Mechanism investigation are important to provide the reason to mechanism based antitumor treatment.[20-22] Cross examination of MCC tumors for transformations of both tumor silencer genes and oncogenes, for example, p53, PTEN, Ras, B-RAF, c-unit, ß-catenin, which are frequently changed and dysregulated in numerous cancers, have neglected to uncover a steady role for any of the genes in MCC.[23] More particularly, looking for receptor tyrosine kinase (RTK) contribution in MCC tumorigenesis, investigations have discovered variable expression of c-kit, VEGFs, PDGFa and PDGFß in MCCs contrasted with ordinary skin. Intriguingly, investigation has demonstrated that the MAP kinase pathway is silent (as exhibited by absence of pathway activation and no ERK phosphorylation) in the majority of MCCs analyzed.[24-25] Recently, the PI3K/AKT and mTOR pathway, the most well-known dysregulated pathway in human cancer, was observed to be upregulated in MCCs, regardless of low transformation rates of PI3K/AKT identified. Collectively, activated pathways will be potential target in mechanism based treatment.[26]

Diagnosis and Treatment modalities

A staging system for MCC was initially proposed by Yieng-pruksawan et al. Stage I was characterized as primary tumor with no proof of local lymph node involvement, stage II as territorial lymph hub involvement, and stage III as the vicinity of systemic metastases.[27-30] Allen et al included tumor size as an alteration of stage I disease, with tumors under 2 cm in breadth named stage IA and those more prominent than 2 cm as stage IIB (Table:1). The general recurrence rate is around 25%, and regional lymph node contribution happens in 52% of cases and distant metastases happen in 34% of patients. MCC in transplant recipients appears to have a more aggressive outcome, with 68% of subjects developing lymph node metastases and 56% dying from disease.[31-33]

Table :1 Immunohistochemistry of Merkel Cell Carcinoma

Stage	Primary Tumor
Ia	Diameter<2 cm
Ib	Diameter>2 cm
II	Loco regional Metastases

III	Distant Metastases

Tumor generally recurs within 2 years of the primary detection, and patient survival is just a matter of months if there are distant metastases.[34] The incessant heterozygous loss of chromosome 10 or the long arm of chromosome 10 in MCC recommends that the tumor silencer PTEN encoded there assumes an important role.[35-38] p53 transformations are incidentally seen in MCC. In 4 of 20 tumors analyzed and in 3 of 8 MCC cell lines p53 mutation were seen. In addition, apoptosis association with p53 depression in MCC xenografts proposes that the regulation of p53 expression may be aggravated in MCC.[39]

The reported 5-year survival rates have shifted from 35% to 80% and appear to depend incredibly on stage, with stage I sickness having survival rates as high as 83%.Various clinical and histologic variables have been referred as a pointers of a poor diagnosis, including patient age, tumor location, large tumor, small cell size, and high mitotic rate.[40-41] Though, the single most vital prognostic component is the stage of the disease, with tumor size prescient of survival in stage I lesions. Surgical excision of the primary lesion with wide edges (1-3 cm) is the prescribed treatment. The Mohs microsurgical technique contrasts positively with standard surgical excision. In anatomic areas where sufficient edges can't be accomplished, radiation treatment for local control has been utilized.[42] Postoperative radiation treatment to the regional lymph node has been appeared to have an expanded survival benefit.

Different chemotherapeutic agents have been utilized as a part of the treatment of MCC, yet results are restricted attributable to the small number of subjects.[43-44] Protocols like those utilized for the treatment of small cell carcinoma of the lung appear to demonstrate the most favorable results, with those containing cisplatin and doxorubicin or 5-fluorouracil. Despite the fact that these tumors show chemo sensitivity, reactions are normally brief.[45] There is by all accounts an increased recurrence time, however no change in general survival has been illustrated. Signs for this technique are extensive injuries, head and neck location, small cell type, or proof of vascular intrusion.For primary tumors without signs of the vicinity of organ metastases complete surgical excision is the fundamental treatment.[46-47] Because of the high rate of local metastases, which can be credited to subclinical satellite metastases, if conceivable, a safety margin of 3 cm ought to be observed. In uncommon location where adjusting the whole situation requires a smaller safety margin, this ought to be repaid by a complete histological investigation of the excised margins including immunohistology to

distinguish CK20 and maybe radiation treatment intercession. At the point when micro metastases are found in the sentinel lymph node, this ought to be trailed by complete lymphadenectomy.[48]

MCCs are generally radiosensitive. Investigations demonstrate that the high local recurrence rate after R0 surgery of the primary tumor alone can be lessened significantly by consolidated loco regional adjuvant radiation treatment (surgical scar with 3 cm safety margin, additionally local lymph node basin.[49] For primary MCCs and local recurrence adjuvant radiation treatment of the tumor region and the regional lymphatic depleting basin is prescribed. The required aggregate dose is thought to be 50 Gy with a solitary dosage of 2 Gy five times weekly. For MCCs at the stage of distant metastases radiation treatment is utilized in a multimodal treatment idea notwithstanding surgical excision or systemic chemotherapy.[50]

This methodology must be applied to the individual case and is typically done with a palliative goal. Despite the fact that MCC is viewed as a chemo sensitive tumor, an evidence based chemotherapy does not yet exist.[51-52] Because of morphological resemblances that are built up for small cell lung cancer have frequently been picked; these incorporate, anthracyclines, antimetabolites, bleomycin, cyclophosphamide, etoposide and platinum derivatives. It gives the idea that complete recuperating is not accomplished in this stage of the ailment.[53] It is further significant that there is clearly no connection between treatment intensity and reaction. In this way, systemic chemotherapy is demonstrated as a palliative measure when distant metastases are available, however, particularly because of the high level of lethality of most chemotherapeutic agents for elderly subjects (restricted hepatic, renal function and hematopoiesis), it must be adjusted to the individual case.[54-55]

Closing Remarks

These clinical perceptions are particularly aggravating as we are just comprehending the pathogenesis of MCC. Hence, the therapeutic methodology is frequently vague; dependable information are accessible for the treatment of loco regional ailment. At the hereditary level, MCC is an impression of the intricate arrangement of mutations resulting in activation of oncogenes combined with inactivation of tumor silencer genes. On the other hand, targeted treatment at the gene level remains a challenge, as there is a refinement between driver mutations that can move the development of cancer and driver transformations on which the tumor cell ceaselessly depends. Also, secondary resistance regularly develops, as saw in

melanoma with BRAF inhibition. Given individual variety in the host immune system as showed by ailment outcome, response to treatment and capacity to metastasize, combination therapy with immunomodulation gets to be pivotal. Latest advances in targeted treatment and immunotherapies in the therapy of metastatic melanoma have actuated use of a comparable approach to deal with other tumor types, including MCC. In this way, scientist anticipate Phase I and Phase II clinical trials with incredible enthusiasm for MCC, as there is an extraordinary requirement for improved treatment.

Conflicts of Interest Statement

The Authors declare no conflicts of interest.

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