Review Article

Multi-Disciplinary Management of Hidradenocarcinoma

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Abstract: Hidradenocarcinoma makes up 6% of eccrine malignancies, and is an uncommon eccrine sweat gland tumour. The etiology is due to genetic alterations and transformation from an existing lesion or hidradenoma. It typically affects the face and scalp, although it can also cause nodal involvement and show up on the trunk, abdomen, or groin. Due to its similarities to other skin tumours, it is challenging to diagnose histopathologically. Therefore, immunohistochemical markers, such as p53, Ki-67, keratin AE1/AE3, and cytokeratin 5/6, are crucial for the diagnoses. There are no prospective randomized trials available to direct treatment of hidradenocarcinoma. A key component of therapy is early diagnoses and case discussion in multidisciplinary tumor board. Wide local excision with clear margins is the mainstay of treatment. Adjuvant treatment like chemo radiation therapy is incorporated if nodal disease or positive margins are present. Recurrences are treated by re-excision followed by adjuvant radiation therapy. Adjuvant hormonal therapy depends on the receptor status of the disease. These tumors have a 50% recurrence rate and up to 60% of the time they metastasize to the brain, bone, lung, liver, mediastinum, or peritoneum in a two-year period. The overall five year survival rate is around 30%. Keeping in view the aggressive course of this disease, research based clinically evident new treatment strategies are the need of time to optimize overall survival and local disease control.

Keywords: Sweat gland tumors, Adnexal tumors, Hidradenocarcinoma, Adjuvant therapy, Multidisciplinary team, Radiation therapy.

INTRODUCTION

There are three main types of sweat glands; eccrine, apocrine and apoeccrine. Eccrine sweat glands are the most numerous sweat gland, distributed all over the body with maximum volume of sweat secretion that is mainly water in composition. They consist of a secretory coil made up of clear, dark or myoepithelial cells and a duct composed of simple tubular epithelium and are present on both hairy and non-hairy regions of the body [1]. The ductal component of eccrine gland gives rise to hidradenoma which has the tendency to transform into malignant hidradenocarcinoma which is a rare and aggressive adnexal malignancy and has both eccrine and apocrine variants [2]. It constitutes 6% of eccrine malignancies. Significant mutations in EGFR, PIK3CA, AKT-1 and TP53 may account for the development of this tumor genetically [3].

Even though the majority of adnexal lesions are benign, their overlapping histological characteristics make them difficult to detect. For working pathologists, these tumours continue to present diagnostic hurdles. The challenge stems from its frequent deviation from standard histology, overlapping features with other form of skin tumours, lack of clinical follow-up, research and ambiguity in identifying benign from malignant [4]. However, they can be differentiated by their inadequate circumscription, irregular boundaries, nuclear atypia, focal necrosis, less sclerotic stroma, and Immunohistochemistry (IHC) [5]. Prospective descriptive analytical study shows that Hidradenocarcinoma is one of the rare forms of malignant scalp tumors in Sub-Saharan Africa [6]. Women are more likely than men to have this illness, especially those who are in their fifth decade of life [7]. It is most commonly found on face and extremities although it can be found on trunk, abdomen and groin as well [8]. It is an extremely aggressive sweat gland tumour that frequently spreads to distant lymph nodes [9]. Overall five-year survival is 30% [10]. A high risk of second primary malignancies has been demonstrated in some studies in addition to the presence of hidradenocarcinoma. Rectal malignancies, non-epithelial skin cancers, and mesothelioma are a few of these. The etiology of these second primaries, however, cannot be determined because hidradenocarcinoma typically develops de-novo or from an already-existing hidradenoma [11].

CLINICAL PRESENTATION

Patients do not show any symptoms for a very long time. The lesion most frequently appears on the face and scalp as a hard, subcutaneous lump or reddish plaque accompanied by ulceration or occasionally by drainage, which is typically serous [12,13]. It can also be found on trunk, abdomen and groin region and less frequently on digits and elbows [8]. The lesion's circumference ranges from 1 to 5 cm, and it may steadily enlarge [14]. However, these tumours are aggressive and 50% of the

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time they return locally; up to 60% of the time they metastasize to the brain, bone, lung, liver, mediastinum, or peritoneum in a two-year period. Hemangioma, lipoma, lymphangioma, melanoma, basal cell carcinoma, Merkel cell carcinoma, squamous cell carcinoma, and other adnexal tumours are among the differential diagnoses for Hidradenocarcinoma [15]. Hidradenocarcinoma may mimic primary breast carcinoma, salivary gland or lung carcinomas or metastatic clear cell carcinomas including thyroid or renal cell carcinomas [16].

DIAGNOSTIC EVALUATION

Biopsy and histopathological diagnosis with immunohistochemistry is essential. Initial investigations may include X-rays or ultrasound of the lesion. CT scan, MRI, and PET/CT scan all play crucial roles in assessing the local and distant metastatic spread of this aggressive tumour. A few case studies have demonstrated the value of the DWI sequence on MRI for accurate diagnosis of hidradenocarcinoma from its benign counterpart, hidradenoma [17].

When it comes to the initial staging and follow-up of this uncommon malignancy, FDG PET/CT can be incredibly helpful as well [18].

IMMUNOHISTOCHEMISTRY

Hallmark IHC markers include p53, Ki-67, keratin AE1/AE3 and cytokeratin 5/6. These tumours exhibit no CEA, S-100, GCDFP-15, EMA, or Bcl-2 staining [17]. Androgen receptor (AR), estrogen receptor (ER), progesterone receptor (PR), EGFR (epidermal growth factor receptor), and HER-2 (human epidermal growth factor receptor 2) positivity in Hidradenocarcinoma varies [19]. However, anti-androgen therapy may be used in apocrine carcinoma subtype because of strong correlation of AR expression in these type of cancers. Her-2/neu might as well be positive is some cases of eccrine histology mainly Hidradenocarcinoma [15,19,20]. They are differentiated from renal cell carcinomas by the absence of CD10 and epithelial membrane antigen [21].

PATTERN OF FAILURE

The length of time the cancer or lesion may grow locally varies greatly, ranging from months to decades. The tumor may eventually exhibit an aggressive clinical history with local expansion or distant metastasis, typically to the lymph nodes. Visceral metastasis, which occurs in 39% and 28% of patients, respectively, is typically preceded by nodal involvement [22].

TREATMENT OF HIDRADENOCARCINOMA

Hidradenocarcinoma is a rare disease. It accounts for 6% of malignant eccrine tumors [2,23]. These tumors are aggressive and recur locally in 50% of cases [10]. Metastases in brain, bone, lung, liver, mediastinal or peritoneal lymph nodes is common and is around 60%. The overall five year survival rate is around 30% [10,24]. There are no prospective randomized trials available to direct treatment of Hidradenocarcinoma. Early diagnoses and case discussion in multidisciplinary tumor board is essential part of treatment [25], as it affects outcome and quality of life of patients [16]. Wide local excision with clear margins is however the mainstay of treatment. Adjuvant treatment like chemo radiation therapy is incorporated if nodal disease or positive margins are present. Recurrences are treated by re-excision followed by adjuvant radiation therapy. Adjuvant hormonal therapy depends on the receptor status of the disease.

SURGERY

Wide surgical resection with 2 cm clear margins and sentinel lymph node evaluation is considered the mainstay of treatment [15]. If a diagnostic surgery has not been done, a second intervention is needed to achieve clear margins and perform regional nodal dissection provided the aggressive nature of disease. Some studies suggest that two step surgery validates margin control and Mohs micrographic surgery provides appreciable local disease control [26]. The surgical oncologist should perform the surgery at the earliest as these tumors have 50% locoregional recurrence and 60% risk of distant metastases [10]. If the patient has not developed distant metastatic disease, clinically positive nodes should be dissected and adjuvant therapy should be offered.

ADJUVANT RADIATION THERAPY

The local recurrence rate following surgery is 10-50% therefore adjuvant radiation therapy is necessary. It depends upon the size of the tumor (>5 cm), margin involvement (<1 cm), anaplastic morphology, angiolymphatic invasion, metastases or unresectable tumor [10, 15, 22]. There is no consensus guidelines regarding radiation therapy doses therefore, discussion in radiation therapy peer review meetings is warranted [27]. It has been seen that doses ranging from 50 Gy to regional nodes to 70 Gy to post-op bed has provided good local control for around 27 to 35 months [28]. Similarly, a case of Hidradenocarcinoma of the parotid region received a 66 Gy of radiation therapy and showed 15 months local control on follow up [29]. A case of young male with Hidradenocarcinoma of scalp with a cervical node was reported. He underwent surgical excision with ipsilateral neck dissection followed by chemotherapy along with radiation, 50 Gy to scalp, and ipsilateral neck with a 10 Gy boost to the deep margin of scalp and Level II neck node and was reported to be disease free at 5 years follow up [23]. R. Rehman reported a case of Hidradenocarcinoma of the abdominal wall arising in the region of prior trauma, which was completely excised with close surgical margins of < 0.1 cm. 20 weeks after surgery the patient received 60 Gy in 30 Fraction External Beam Radiation Therapy via a 3D conformal wedge pair of right and left anterior and posterior oblique fields respectively with a 5 mm bolus. The therapy was well tolerated with no long-term toxicities and local recurrence six months after radiation [30].

CHEMOTHERAPY

The role of chemotherapy in treating Hidradenocarcinoma is indiscernible. Chemotherapy may provide some benefit in the scenario of metastatic or unresectable disease. A case series of 7 cases of metastatic Hidradenocarcinoma was published which showed that only one out of six patients who had lymph nodal metastasis and who received concurrent chemo radiation therapy showed a disease free survival of 45 months [31]. Multiple chemotherapy regimens have been used including 5-Fluorouracil and Capecitabine as first line agents and doxorubicin, carboplatin, cyclophosphamide, vincristine and bleomycin as second line chemotherapeutic agents and have shown more than 50% disease remission but it is a single patient study and more such cases need to be reported to reach a consensus [23, 27, 32]. Similarly, one case with multiple metastatic deposits in an elderly was reported who was administered vincristine and bleomycin but the patient did not survive and died within a few months [27]. S. Korbi reported a case of Hidradenocarcinoma of the thigh with multiple relapses and metastatic deposit in the lung treated by oral Sunitinib as fourth line chemotherapy and it showed a fast clinical response in two months as well as a good objective response on the metastatic deposit [33]. H. Obermann has reported a case of left flank cutaneous Hidradenocarcinoma with pulmonary, osseous, and cutaneous metastasis in an elderly woman who underwent stereotactic radiation therapy for cerebral lesions as well as next-generation targeted sequencing of primary tumor for finding potential targeted therapy. She was then treated on the off-label first line, anti-PD-1 immunotherapy, Nivolumab 240 mg q2w. 13 cycles of immunotherapy showed primary as well as minimal residual disease in metastatic deposits [34]. Hence the role of chemotherapy as an adjunctive therapy still remains unclear.

HORMONAL THERAPY

Hormonal and targeted therapies including Tamoxifen and Trastuzumab have proven useful in Estrogen receptor positive and Her 2 neu amplified cases respectively [16].

The use of targeted therapy and anti-androgen therapy is in the clinical testing phase and clinical trials are awaited to reach a consensus regarding treatment with these modalities [22, 33]. A novel treatment option of electro-chemotherapy that involves treatment with both loco regional and IV administration of very low-dose bleomycin or cisplatin with electroporation of cellular membranes has been discovered. This method improves direct penetration and saturation of chemotherapeutic agents in the cytoplasm and hence enhances cytotoxicity. This treatment modality can also be combined with radiation therapy for various skin and adnexal tumors [34].

CONCLUSION

Hidradenocarcinoma is a rare but aggressive sweat gland tumor with a high potential for development of loco regional and distant metastasis. Diagnosis is based on histological and immunohistochemical evaluation. Negative margin surgery followed by discussion in multi-disciplinary tumor board for adjuvant therapy is the mainstay of treatment. Keeping in view the aggressive course of this disease, research based clinically evident new treatment strategies are the need of time to optimize overall survival and local disease control.

AUTHORS' CONTRIBUTION

- **Mariam Hina**: Substantial contribution to the conception & design of the work along with drafting, revising and critically analyzing for significant intellectual content and final approval.
- **Asra Hassan and Maria Tariq**: Drafting, revising and critically analyzing for significant intellectual content.
- **Muhammad Muaz Abbasi and Muneeb Uddin Karim**: Concept and design of the work, revising and final approval.

CONFLICT OF INTEREST

Declared none.

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