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Hidradenocarcinoma: A Rare Skin Disease

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Abstract

Hidradenocarcinoma (HAC) also known as ''sweat gland tumor'' is an aggressive, uncommon, highly malignant, adnexal tumor derived from the intradermal duct of eccrine sweat glands. It is said to be aggressive as it has a high risk of local recurrence (50%–75%) and a high potential to metastasize to nearby lymph nodes or to other distant sites. Hidradenocarcinoma has other recognized variants which are known by different names such as Malignant Acrospiroma, Nodular Hidradenocarcinoma, Clear cell Hidradenocarcinoma, Malignant Nodular Hidradenoma, Malignant Clear Cell Hidradenoma, clear cell eccrine carcinoma or simply sweat gland tumor. However, the term Hidradenocarcinoma (HAC) is the recommended name. This malignant tumor arises from the eccrine glands which are located in sun-exposed locations. These malignancies exhibit a high reactivity to eccrine enzymatic stains and their morphologic features are seen under the electron microscope, so that's why they are known to originate in the sweat glands. The occurrence rate is about 0.001% of all malignant tumors and Hidradenocarcinoma accounts for approximately 6% of malignant eccrine tumors, which in turn are found in 1:13,000 skin biopsies and <0.001% of all skin cancers. They usually appear de novo on healthy skin, or sometimes malignant transformation from their benign form. In 1865, French pathologist Victor Andre Cornil described the first case of sweat gland cancer. Hidradenocarcinoma (HAC) was first reported in 1948 in Brazil and was first described as a clear cell eccrine carcinoma by Keasby and Hadley in 1954. When Keasby first described this tumor in 1954 he found only 3 cases of hidradenocarcinoma among 235 sweat gland tumors.

Keywords: Tumor, Carcinoma, Hidradenocarcinoma, Hidradenoma, Malignant.

INTRODUCTION

Hidradenocarcinomas (HACs) are difficult to differentiate clinically, hence histological evaluation is required [1]. All sections stained with hematoxylin and eosin, Best's carmine, and the periodic acid-Schiff technique (PAS) [2] which resulted in Hidradenocarcinoma manifests as a low-grade, hard, and asymptomatic intradermal nodule of 1–5 cm in diameter. It is covered by purple, pink, or blue-colored lesions that are either intact or infrequently ulcerated [3]. Figure 1 depicts Histopathology of the excised tumor showing polygonal cells, Kavya A, 2024. This low-grade malignant solid tumor has negative margins [4]. It is situated from the dermis to the subcutaneous tissue [5]. The shape of the tumor is a single, non-mobile, firm nodule with no pain(asymptomatic) [5], or can be multi-lobular, ulcerated, and cracked with cystic spaces, generally from pleomorphic round to oval with two ductal structures [6, 7] there is lack of circumscription (i.e. poorly circumscribed tumor) [6, 8]. The tumor growth pattern is infiltrative [8]; deep extension [8]; the size of the tumor increases steadily, and the tumor is often followed by ulcers [5]. The nucleus is generally vesicular having 1-2 prominent nucleoli along with a clear to slightly eosinophilic cytoplasm [5] and other histological features are necrosis, vascular invasion, and

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perineural invasion [7, 8], clefts between tumor and stroma [9]. The preauricular lymph node may also show reactive hyperplasia [7]. Tumors have increased mitotic activity i.e. <4 mitoses per 10 high–power fields (HPFs) [8].

There are two sorts of cells in general [8].

1. Polyhedral cells with slightly basophilic cytoplasm
2. Glycogen-rich round clear cells

Tubular lumina have varying sizes and the cystic spaces which are present within the lobule are filled with eosinophilic secretion. The Stroma shows mild to moderate infiltrate of lymphocytes and eosinophils [7].

Sometimes the benign counterpart of hidradenoma starts showing focal atypical features like lack of circumscription, necrosis, nuclear pleomorphism, or increased mitotic activity. These tumors are called as Atypical Hidradenoma and these Atypical Hidradenomas have very high malignant potential [8]

The primary location for this uncommon malignant intradermal tumor is the head, neck, and trunk regions, and is rarely found on the distal extremities including the eyelid, scalp, lip, neck, chest wall, breast, back, leg, toe, hand, orbit, nose, vulva, and ankle.

Since this tumor has an insidious growth pattern it is most commonly diagnosed during the fifth to seventh decade of life, but it can affect people of any age, as seen by a case report of a 15-month-old patient, with a similar frequency of occurrence in males and females, but it is also suggested that there is a higher frequency of occurrence of Hidradenocarcinoma in women. As previously said, hidradenocarcinoma is diagnosed late, owing to the fact that the disease remains asymptomatic for a long time. Its prognosis factor is usually poor, and the disease-free survival rate within 5 years is <30% according to literature. Therefore, early detection and diagnosis, surgical treatment with wide excision or Mohs micrographic surgery are recommended for a favorable prognosis.

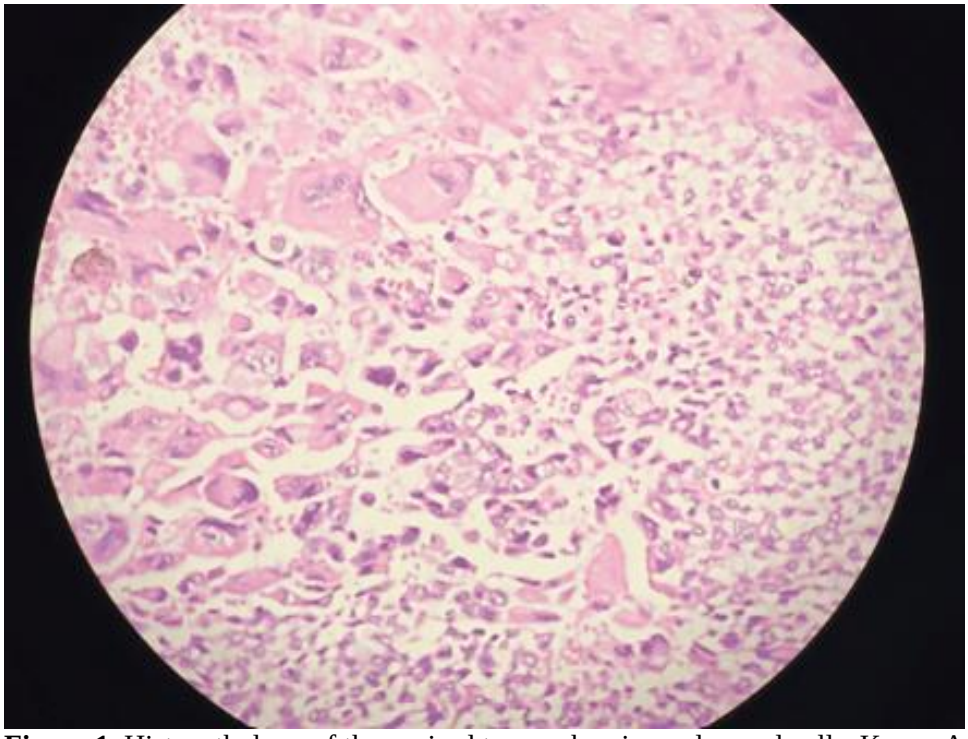

Figure 1. Histopathology of the excised tumor showing polygonal cells, Kavya A, 2024.

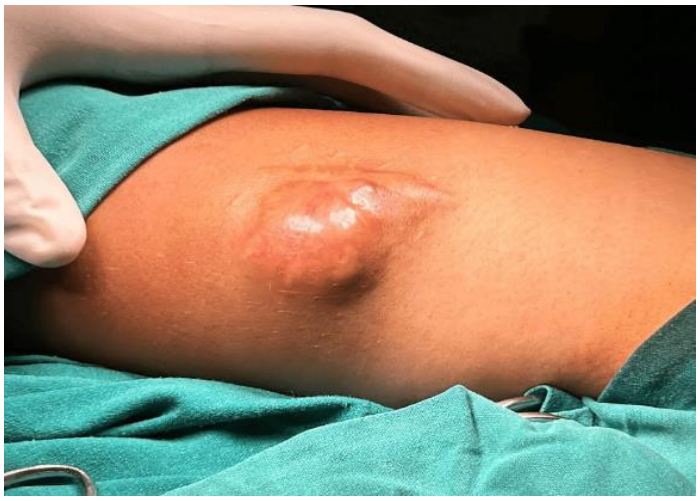

Figure 2. A Clinical presentation of hidradenocarcinoma over the posterolateral aspect of the left arm, Kavya A, 2024.

Metastasis

Since these tumors are histologically malignant so they have high metastatic potential [10] These tumors are known for their local recurrence [11] and they have the higher incidence of regional and distant metastasis to the surrounding lymph nodes or to other distant sites [4, 12, 13] The majority of reports suggested that distant metastasis occurs after tumor recurrence and ultimately leads to death. The local recurrence rate after surgical excision is around 50%, and over 60% of patients show metastasis to the lymph nodes, skin,bones, and internal organs[5, 11, 10]. The first case of metastasis was of a 32-year old man who had a history of the non-healing ulcerative lesion under his right axilla, on examination and after doing an excisional biopsy of the axillary lesion showed a poorly differentiated HA, positron emission tomographic computed tomography (PET CT) scan showed that the tumor got metastasized to bilateral supraclavicular lymph nodes and to the posterior right 5th rib [10].

Hidradenoma vs Hidradenocarcinoma

Hidradenocarcinoma (HAC) is often confused with Hidradenoma (HA), even histologically [1] as both these tumors are somewhat related with each other. But there are some differences among these tumors as a result of which they are known under different names.

Basically, in Hidradenoma if the suffix carcinoma is used then it indicates the malignant form of Hidradenoma [14]. Figure 2 shows clinical presentation of hidradenocarcinoma over the posterolateral aspect of the left arm, Kavya A, 2024.

The main differences between Hidradenoma and Hidradenocarcinoma are described below.

1. Hidradenoma is an uncommon benign tumor of sweat gland origin [15]. It is known by different names, including nodular hidradenoma, solid-cystic hidradenoma, Poroidhidradenoma, and acrospiroma whereas Hidradenocarcinoma is the malignant form of hidradenoma and is known by Malignant Acrospiroma, Nodular Hidradenocarcinoma, Clear cell Hidradenocarcinoma, Malignant Nodular Hidradenoma, Malignant Clear Cell Hidradenoma, clear cell eccrine carcinoma or simply the sweat gland tumor [16].
2. Malignant Hidradenoma differs from benign hidradenoma due to the following histological features that include-poor outline, infiltrative growth pattern, deep extension, necrosis, perineural invasion, vascular invasion, nuclear pleomorphism, and increased mitotic counts [16, 17].
3. Benign nodular Hidradenoma is usually well-formed and small in size whereas Malignant nodular Hidradenoma is larger in size and has an asymmetrical growth pattern [18].

4. In hidradenoma tumor cells a t(11;19)(q14–q21;p13–p12) translocation occurs due to a fusion of mucoepidermoid carcinoma translocated 1 (METC1) gene andmastermind-like 2 (MAML2) gene but in hidradenocarcinomas mutations of the TP53 gene and Her2/neu gene amplification occurs [19].
5. Hidradenoma cells always show negativity for p53 in immunohistochemistry but Hidradenocarcinoma cells may be positive/negative for p53 [19].
6. The treatment for benign nodular Hidradenoma is the primary surgical excision of a tumor while the treatment for malignant Hidradenoma is tumor excision with 2 cm tumor-free surgical margins due to the risk of lymphatic metastasis [18].

Genes

The tumor cells of Hidradenocarcinoma generally show mutations of the TP53 gene [19] and gene amplification of Her2/neu locus [19], also in some cases there is overexpression of p53, p63, p73 and delta Np63 [20], A mutation in PIK3Ca was also identified [10].

The Fluorescence in situ hybridization (FISH) technique is performed for HER2/neu gene amplification, FISH was only performed in cases that were focally positive 2+ for HER2/neu [19].

In Tp53 there is generally point mutation or non-sense mutation in the exon region of the gene. A case demonstrated a homozygous point mutation at c.818 in exon which resulted in an amino acid exchange at p.R273H. Another case demonstrated a nonsense mutation in exon 6 mainly at c.586 and c.637 which lead to premature stop codons p.R196X and p.R213X [19].

The expression of p53 can be interpreted with the help of immunohistochemistry. The tumor cells of Hidradenocarcinoma mostly show positive immunochemical reaction for p53. The lower positivity levels of p53 do not correlation with tumor grade (i.e whether it is of low grade or high grade). A case report demonstrated a high-grade tumor which showed negative immunohistochemicalreaction [20].

TP53 mutation and PIK3Ca mutation stains strongly for EGFR by immunohistochemistry but none of them had EGFR amplification by FISH [20].

Immunohistochemistry

Morphological assessment is of great importance for skin adnexal lesions. So that's why immunohistochemical staining can be used as an aid [21]. The diagnosis of hidradenocarcinoma is complex as there are no defined immunohistochemical features for its diagnosis; the diagnosis of Hidradenocarcinoma is facilitated with help of certain markers [22].

Hidradenocarcinoma shows strong positivity for epithelial markers (10) like Cytokeratin 5/6 (7), Cytokeratin 7 (CK7), Epithelial Membrane Antigen (EMA), Carcinoembryonic Antigen (CEA), CAM 5.2, CAM 19 [9] and may show positivity for p63, Vimentin, GCDFP-15 and shows negative results for the S100 protein, and increased mitotic activity and proliferative index can be determined with the help of Ki-67 staining [7, 23]

- Ki-67 is a proliferation marker that has a pattern for nuclear positivity, This marker helps in identifying the proliferative index and it also helps in differentiating between benign and potentially malignant tumors [24].
- p53 is a tumor suppressor gene, but sometimes because of ultra-violet rays there is overexpression of wild type p53 gene or mutation in p53 because of this mutation an unstable protein product is released which gets detected immunohistochemically, so p53 is also used as a marker and it mostly stains positively for Hidradenocarcinoma but there are some rare cases where the high-grade tumor may also stain negatively for p53 [25]. P53 positivity along with Ki-67 positivity indicates malignancy and it differentiates between Hidradenoma and Hidradenocarcinoma [24].

- Bcl-2 can also be used as a marker as it is an anti-apoptotic protein that is present on the outer membrane of mitochondria. This protein inhibits programmed cell death. Bcl-2 may stain positive [24].

Hidradenocarcinoma also shows positivity for various receptors like HER-2 (human epidermal growth factor receptor), estrogen receptor (ER), progesterone receptor (PR), EGFR (epidermal growth factor receptors), and androgen receptor (AR) [25]. The FISH technique is used for the detection of trisomy and polysomy of epidermal growth factor receptor [25].

The immunohistochemical markers produce various proteins and these proteins are immunostained and various test are used to determine the extent of expression of these immunostained proteins, example-HercepTest is used for interpreting the extent of expression of the c-erb-2 protein, the protein is immunostained negative if the Hercep test result is 0 or 1, weakly positive if the result is 2+ and strongly positive if the result is 3+. Another example is p53, if 5% of cells are immunostained positive then the expression of p53 is negative, if 5%–25% of cells are immunostained positive then the expression of p53 is focally positive 1+& if 26%–50% of cells are immunostained positive then p53 expression is focally positive 2+, and similarly if 50% of cells are immunostained positive then the expression is focally positive 3+ [19].

REVIEW OF LITERATURE

Case 1

Lim et.al reported a case of Hidradenocarcinoma on the Orbit of a 40-year-old man [5]**,** The patient had exophthalmos for 8 months and his left eye's vision was decreased for 1 month. Visual field defect, reduced vision (0.2), and raised intraocular pressure (20 mmHg) were discovered during an ophthalmological examination of the left eye. A well-enhancing tumor in the left orbit was discovered on computed tomography (CT) scan, with focal bone loss of the lateral orbital wall and focal invasion into the anterior section of the left cavernous sinus. A localized mass measuring 4.5× x2.2×3.6 cm^3 in size, iso-signal intensity on T1 and T2-weighted images, and heterogeneous enhancement in the lateral aspect of the left orbit were discovered on magnetic resonance imaging (MRI). The lateral orbital wall had focal bone destruction. The mass spread over the temporalis muscle, superior orbital fissure, and cavernous sinus. They performed a biopsy and discovered that the tumor was hidradenocarcinoma; as a result, they planned a surgical resection with enucleation of the eyeball. The modified lateral supraorbital technique was used to perform the complete resection. The tumor appeared to be hyperemic and yellowish in appearance. It was difficult to separate the optic nerve from the tumor. Fat packing and enucleation of the left eyeball were performed. An instant postoperative MRI revealed that there was no remaining tumor. In the dermis, ill-defined multilobular tumors were seen in abundance in a biopsy of the tissue removed by surgery. The tumors were surrounded by a pseudo capsule made up of fibrotic stroma, and there was also a cystic space induced by tumor necrosis. The tumor cells had a clear cytoplasm and were round to polygonal in form. Mitosis and cellular atypia were commonly noticed. They also performed an immunohistochemical analysis which resulted in tumors being positive for epithelial membrane antigen (EMA), vimentin, cytokeratin, S-100, and high proliferation labeling index (Ki-67 30%) but They were negative for carcinoembryonic antigen (CEA) and gross cystic disease fluid protein 15 (GCDFP-15). They identified hidradenocarcinoma on the left upper eyelid extending into the left cavernous sinus with orbital bone damage based on these histological results and imaging examinations. Because of the tumor's features, such as a high recurrence rate and widespread metastasis, adjuvant radiation with a total dosage of 5,400 cGy/27 fraction was used. The patient's condition had been stable for four months, with no recurrences or problems. But 5 months after the surgery, the patient developed a sudden right eye visual complaint. Visual field defect, reduced vision (only light perception), and 16 mmHg intraocular pressure were discovered during an ophthalmological examination of the right eye. Focal atrophy in the retina was discovered as a consequence of the mydriatic test. In addition, the visual evoked potential result showed that the P1 and P3 latency were delayed, and the

electroretinography result showed that the rod function was reduced. However, the multi-focus electroretinogram was normal, and There was no evidence of recurrence or metastasis on MRI and positron emission tomography (PET)-CT imaging. They hypothesized that the visual problem was linked to cancer-related retinopathy (CAR). They also began systemic steroid therapy as well as adjuvant chemotherapy. Cisplatin and 5-fluorouracil was given to the patient. The patient's cognitive ability deteriorated during the first chemotherapy cycle, and cranial nerve palsy (III, IV, VI) emerged. They recommended an MRI examination and the second cycle of chemotherapy, but the patient refused the additional treatment. The patient died after 7 months**.**

Case 2

Wan et al. reported a rare case of tumor on the first web space of the dorsum of the left hand in a 57-year-old male [3], It is a rare case as the dorsum of hand very less possibility of eccrine gland tumor as very less sweat glands are present there. This solid painless mass of cells has been present on the dorsum of the left hand for the past 10 years, almost 5 years ago the man resected the tumor from a local clinic but the mass recurred and it has increased in size. The tumor was non-tender upon palpation. The histology of the tumor indicated that the tumor consisted of irregular-shaped solid sheets and infiltrative clusters of different sizes. The surface of the tumor had ulcers and multifocal ischemic necrosis. Generally, two types of cancer cells were observed, the first type of cells had clear cytoplasm and distinct cell membrane, the nucleus was moderately pleomorphic in nature with vesicular chromatin distribution, and prominent nucleoli were seen. Another type of tumor cells had basaloid in appearance along with scanty eosinophilic cytoplasm, and small round ductal structures. Physical examination was conducted to check wheatear there is any case of regional metastasis and no associated case of cubital or axillar lymphadenopathy was reported no case of distant metastasis was detected after Positron emission tomography-CT (PET-CT). On immunohistochemical staining, the tumor cells positively reacted for p63, CK5/6, and the epithelial membrane antigen (EMA). P53 was overexpressed, and the Ki-67 labeling index was reported to be 70%. The positive expression of p53 and Ki-67 indicated that it was hidradenocarcinoma. The tumor was surgically resected and after resection malignant cells were found near the surgical resection these cells were also resected and the defect was covered with a skin graft which was extracted from the groin area.

Case 3

Cleaveland et al. reported a case of a rare presentation of hidradenocarcinoma within the penis [26]. It was a report of a 46-year-old man. He had a lump of cyst on the shaft of his penis. He had no prior medical history. On inspection, a mobile nodule measuring 8 mm in diameter was founded over the left side of the distal shaft of the penis, proximal to the coronal sulcus near the frenulum. There were no palpable lymph nodes found. Further wide local excision was performed. A multinodular, solid-cystic, and poorly differentiated carcinoma measuring 15 mm by 10 mm with a border of less than 5 mm was discovered on histological analysis within the dermis. The tumor resembled a high-grade and malignant cutaneous adnexal tumor of the hidradenocarcinoma sub-type upon closer inspection. Large lobulated islands of basaloid cells, an abundance of mitotic figures, and several foci of necrosis were all present. The perineal invasion was not present, however lymphovascular invasion was present. The tumor cells stained strongly for p16, p63, s100, MIB-1, and MNF-116 on immunohistochemical analysis, with weaker staining for 34E12 and sparse localized staining for AE1/3, CK14, BerEP4, and epithelial membrane antigen (EMA). They also performed cytogenetic analysis to exclude adenoid cystic cancer by looking for MYB-NFIB gene fusion products, which came up to be negative. After a debate at a supra-regional multi-disciplinary cancer meeting, surveillance was commenced because there was no evidence of metastatic illness on imaging. He suffered a local recurrence two years later, which was treated with a partial penectomy. Histological analysis indicated a lesion in the corporal tissue and in one area of the para-urethral corpus spongiosum of the glans, which was consistent with his past condition. Vascular invasion and resection margins were there. The results of a subsequent bilateral radical groin node dissection were negative for the disease, but he suffered a recurrence on the penile stump a year later. He had total penectomy and a perineal urethrostomy after that. On the

left side of the corpus cavernosum, the histological investigation revealed a single well-circumscribed focus of poorly differentiated adenocarcinoma. He had small lung metastases two months later, which were not noticed earlier. He then suffered a left inguinal node recurrence, 18 months later which was further removed. His left groin and lung were treated with radiotherapy. A lesion compatible with his past condition was discovered on histological evaluation. Finally, irradiation was done to treat right tibial metastasis.

Case 4

Singh et al. reported the first case of hidradenocarcinoma in the buttock region, a painless mass was found on the left buttock of a 61-year-old woman [4], this mass has been present for so many years but the size has increased over the period of past 6 months. This mass was violaceous fungating and non-tender to palpation. The histology showed a low-grade malignant adnexal tumor with negative margins. The examination was conducted to see whether there is any regional metastasis and upon examination, no associated inguinal lymphadenopathy was detected. Positron emission tomography and computed tomography revealed no evidence of distant metastasis, computed tomography (CT) scan, and a biopsy indicated the mass in the left upper buttock area is associated with feeding vessels. Immunohistochemistry showed a positive stain for estrogen receptor, and progesterone receptor and negative for HER-2/neu. The tumor was surgically excised with grossly normal margins and the tissue was oriented.

Case 5

OHTA et al. reported a case of a Nodular Hidradenocarcinoma on the Scalp of a 27-year-old woman [27], The patient was evaluated with a nodular lesion of 10 months duration. The patient had gone to a local clinic three months before for an asymptomatic scalp lump, and it was recommended that the mass be surgically removed under the diagnosis of lipoma, fibroma, or another neoplasm. For the removal, she was referred to their hospital. On physical examination, a 3*3 cm firm, smoothly raised lump with normal scalp skin on the vertex was discovered with no swollen lymph nodes found. The patient had no previous medical issues or family history. A CT scan of the occipital region revealed homogeneous tumors of low-density covered with the skin but no indication of metastatic illness was there. Under local anesthesia, they removed the tumor and closed the skin with a primary suture. The tumor appeared pale and a little firm under the microscope, and it resembled a lymph node. When viewed under the microscope the lesion seemed to be a well-circumscribed, lobulated intradermal lump with capsule-like tissues that extended into the subcutaneous tissue. There was no evidence of an epidermal connection between the tumor and the skin, and many different-sized cystic cavities in the tumor nodule were present as a result of tumor necrosis. The tumor cells had a lobulated growth pattern with tubular differentiation, monomorphic hyperchromatic nuclei, and scarcely visible cytoplasms. A pseudocapsule developed around the desmoplastic stroma. The presence of cellular atypia and mitotic figures was common. The diagnosis of nodular hidradenocarcinoma was confirmed by the final pathologic study. There were no further metastases discovered. Around the prior scar, a 1.5-cm radial cutaneous margin was created. A rotating flap was used to close the defect. The surgical wounds recovered quickly. There was no adjuvant therapy given. The patient did well twenty-four months following the surgery and had no evidence of local recurrence or metastatic disease.

Case 6

Elbenaye et al. reported a fatal hidradenocarcinoma of the scalp in a 37-year-old man [28], the man had retroauricular skin nodule on his right side for the last 4 months. That nodule rapidly increased in size. Biopsy was done and histopathological was conducted along with that immunohistochemical staining was done and the tumor gets stained positively for cytokeratin, pathological study diagnosed the presence of Hidradenocarcinoma. The tumor was at the T2N0M0 stage which meant that the primary tumor has largely grown in size with no case of its presence in regional lymph nodes and no case of metastasis. The tumor was resected at this stage along with the superficial muscle. Again two months later the patient got diagnosed with cervical and right submandibular lymph nodes that were

metastatic in nature, skin examination demonstrated the reoccurrence of the tumor at the primary site. Patient treatment was started and deep cervical and submandibular lymph node dissection was performed and adjuvant radiotherapy was planned, while the treatment was going on the patient was lost to follow-up for 4 months, later on, the patient started attending the emergency department along and his consciousness disturbed due to cavernous sinus thrombosis. Unfortunately, the patient died several days later.

Case 7

Khalil et al. reported a case of malignant eccrine hidradenoma of the neck causing acute heart failure [29], A 73-year-old Caucasian male reported to the emergency room with progressive dyspnoea over an 8-weeks period accompanying chest pain on exertion. He also had a massive fungating, stinky growth on the right side of his neck that had been there for about 12 years and had been progressively growing in size over the last two years. He was a former smoker with no prior medical history. He was determined to be clinically anemic, in heart failure, and with acute renal failure upon assessment. He had a large lump (10/10 cm) on the right side of his neck's posterior triangle, which had ulcerated through the skin and had multiple active bleeding spots. There was no swelling of lymph nodes on his neck, and his cranial nerves were healthy. His complete blood count revealed 5.7 g/dl hemoglobin, leucocytosis, and abnormal liver function tests. The medical practitioner directed him to the ENT department after addressing his serious medical condition. Adenoid cystic basal cell carcinoma of the skin was diagnosed after a biopsy of the neck lesion. There were no metastases found on an ultrasound of his abdomen. A CT scan of his chest and abdomen revealed a 1.5 cm lesion at the base of his left lung. The lung lesion had modest atypia with no conclusive cancer cells, according to a CT-guided biopsy. The lump was found to be superficial and lateral to the sternocleidomastoid muscle on an MRI examination of the neck. Surgery was determined to be the optimum treatment after consultation with their multidisciplinary team of head and neck oncologists. He received total removal of the lesion and repair with a deltopectoral skin flap approach. The histology of the specimen that had been sent for a second opinion was reported to be a nodular eccrine hidradenocarcinoma. He was given adjuvant radiotherapy to reduce the likelihood of local recurrence. A subsequent CT scan of the chest revealed that the lesion in the lung had decreased in size, indicating the presence of inflammation. There was no sign of loco regional recurrence two years after surgery, and the aesthetic look was outstanding.

Case 8

Son et al. reported a case where a thickened nail bed was present on the left index finger of a 76-year-old woman and it had darkish discoloration that was increasing gradually [30, 31], the nail had mild tenderness and a small amount of transparent fluid discharged from her fingertips. Since the patient was old and had a medical condition of diabetes, initially it was thought that she had a chronic fungal infection, and a topical antifungal ointment was prescribed. The biopsy of the mass margin was done and the first histopathology was conducted, the pathological result indicated that the tumor had chronic active inflammation with no fungal hyphae, but this case was misdiagnosed as chronic active inflammation with severe plasma cell infiltration the reason for this was that very less volume specimen (i.e epidermis and dermis) got exacted in the biopsy. Then again second partial biopsy was done under the influence of local anesthesia and again histopathology of that sample was conducted which showed that the lesion was a poorly circumscribed intradermal nodule with infiltrative growth. The tumor cells had morphology the same as that of nodular hidradenoma. The tumor cells were highly atypical and had small lobules, nests and cords, and partly cystic portion. Tumor cells had nuclear hyperchromatism, prominent nucleoli, and abundant clear cytoplasm with no vascular or perineural invasion, the tumor cells reported a slight increase in Mitotic activity. Immunohistochemistry was conducted, The tumor cells strongly stained positive for p63 and focal positive for cytokeratin, but the tumor stained negative for all the epithelial markers [EMA, CEA, CAM5.2, CK7)], melanocytic markers (HMB45, Tyrosinase, Melan A, S-100), clear cell renal cell carcinoma markers and Smooth Muscle actin (SMA). The Ki-67 proliferating index was 3% only. All

the pathological analyses lead to the confirmation that it was a case of Hidradenocarcinoma. Physical examination was conducted to check regional metastasis and radiological examination like PET –CT was conducted to check distant metastasis and no case of metastasis was detected so no chemotherapy or radiotherapy was performed. Surgery was performed and the tumor was completely excised under local anesthesia, no case of local recurrence or distant metastasis was observed after 1 year follow-up of the surgery.

DISCUSSION

The presented case studies demonstrate the diverse clinical presentations and management strategies for hidradenocarcinoma, a rare malignant adnexal tumor of the sweat glands. The cases span a wide range of anatomical locations, including the orbit, hand, penis, buttock, scalp, neck, and finger. The tumors exhibited varying histological features, such as clear cytoplasm, basaloid appearance, and cystic spaces, as well as different immunohistochemical profiles, including positive staining for p63, CK5/6, EMA, and p53. The patients underwent different treatment modalities, including surgical resection with or without adjuvant therapy, depending on the extent of the disease and the presence of metastasis. The outcomes varied, with some patients experiencing local recurrence, distant metastasis, or even death, while others remained disease-free after treatment. These cases highlight the importance of early diagnosis, accurate histopathological evaluation, and individualized treatment planning in the management of hidradenocarcinoma.

Treatment

There are no established treatment options for the management of Hidradenocarcinoma, till date as it is very difficult to treat the tumor due to its aggressive clinical characteristics [5, 23].

Wide Surgical excision (complete resection) with negative margins is considered as the treatment of choice wherever possible. After the diagnosis, it is recommended to perform wide surgical excision as soon as possible as the tumor is known to recur locally and metastasize to bone, lymph nodes, or visceral organs [5, 12, 25].

HDC manifests clinically as a single, painless skin nodule, commonly in the head and neck, measuring 0.5 to 2.5 cm in diameter and capable of rapidly expanding to a diameter of roughly 10 cm after inadequate excision or trauma over many weeks. Because of the potential of rapid progression following trauma, any nodular lesion suggestive of HDC that measures less than 2.5 cm should be treated by biopsyresection rather than simple biopsy, which must be quickly followed by complete resection if it is undertaken. The French association of otorhinolaryngology's most recent guidelines prescribe a lateral resection margin of 10 to 20 mm with deep subdermis margins, reaching but sparing the fascia (forehead), perichondrium (ear, nose), and periosteum [28].

Further different types of surgeries are there which include-Classical cancer surgery, two-step surgery which may provide better margin control, and Mohs micrographic surgery through which excellent control could be achieved [25]. Mohs micrographic surgery (MMS) with or without wide local excision is preferred as the standard treatment of non-melanoma skin cancer [32]. Among the surgical events, Mohs micrographic surgery has been shown to have the highest cure rates for Non-Melanoma Skin Cancer (NMSC) because it allows for microscopic examination of all margins while also preserving the most amount of surrounding healthy tissue, whereas surgical excision only examines the margins by random vertical sections, resulting in only 1% of the margins being examined [33].

However, in those cases where surgery is impossible, additional treatment options such as Adjuvant therapies (radiation and chemotherapy) should be considered, especially in the case of recurrent tumors, positive margins, and metastasis to the lymph nodes [1]. High doses of radiation (RT) ranging from 50 to 70 Gy are recommended. Further various chemotherapy regimens include First line, chemotherapeutic agents such as a 5-fluorouracil-based regimen and capecitabine (oral 5-

fluorouracil); and second line agents , such as, platins, doxorubicin, cyclophosphamide, vincristine, and bleomycin. The role of chemotherapy is unclear either alone or in conjugation with radiotherapy as studies have shown that even after this treatment disease progression was there [25].

Also combined treatment with wide excision and adjuvant radiotherapy is considered to be appropriate [5]

Electro chemotherapy (ECT) is also a cancer treatment approach that includes a combination of intravenous administration of extremely low doses of an antineoplastic agent (typically bleomycin or cisplatin) with cellular membrane electroporation. With the help of Electroporation chemo drugs are penetrated into the cytoplasm which further leads to higher levels of cytotoxicity in cancer cells with fewer adverse effects. ECT is a non-thermal, safe, and well-tolerated therapy option for all types of solid tumors, notably in the cutaneous and subcutaneous areas. According to Shil et al. and Kranijc et al. ECT works in synergism with RT or a combination of ECT+ RT+ systemic chemotherapy. External RT in conjunction with ECT-bleomycin was first described in humans by the Hellenic Group of Electrochemotherapy. As a result, the combination therapy of ECT and RT can provide outstanding therapeutic results for all forms of skin malignancies in the head and neck area [25].

Further targeted therapy such as trastuzumab is effective for the management of metastatic hidradenocarcinoma. Other targeted therapy include Akt/PI3K/mTOR pathway inhibitors and hormonal agents like antiandrogens [25].

Still the management of this uncommon tumor is not well defined, which is why the outcome is poor despite the use of multiple treatment options [23]. Therefore, timely diagnosis is crucial for both the treatment result and the patient's quality life. Also, patients should be monitored monthly. With each follow-up, the patients should be checked for local recurrence, radiation toxicity, and metastatic spread. In case of clinicalsuspicion, radiological examinations including x-ray, PET scan, and CT scan may be considered [25].

Further research is necessary in order to better understand the most effective treatment method and to improve the overall prognosis rate [22].

CONCLUSION

In conclusion, Hidradenocarcinoma (HAC) is an aggressive, malignant tumor derived from the intradermal duct of eccrine sweat glands. It is characterized by a high risk of local recurrence and metastasis to nearby lymph nodes or distant sites. HAC typically presents as a single, painless nodule on sun-exposed areas of the skin, and it is often diagnosed late due to its insidious growth pattern.

Histologically, HAC is characterized by a low-grade, hard, and asymptomatic intradermal nodule with negative margins. The tumor has an infiltrative growth pattern, deep extensive, and may exhibit necrosis, vascular invasion, and perineural invasion. Immunohistochemical staining is used to aid in diagnosis, with HAC showing strong positivity for epithelial markers and various receptors.

Treatment options for HAC are limited, with wide surgical excision being the preferred option. Mohs micrographic sugery is recommended for its high cure rates and ability to preserve surrounding healthy tissue. Adjuvant therapies such as radiation and chemotherapy may be considered in cases of recurrent tumors, positive margins, or metastasis. Targeted therapies such as trastuzumab and Akt/PI3K/mTOR pathway inhibitors may also be effective in managing metastatic HAC.

Overall, the management of HAC remains challenging, and further research is needed to improve treatment outcomes and prognosis rates. Early detection and diagnosis are crucial for a favorable prognosis, and patients should be monitored closely for local recurrence and metastatic spread.

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