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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 were stained with hematoxylin and eosin, Best's carmine, and the periodic acid-Schiff (PAS) technique [2], which resulted in Hidradenocarcinoma manifesting as a low-grade, hard, and asymptomatic intradermal nodule 1–5 cm in diameter. It is covered by purple, pink, or blue lesions that are either intact or infrequently ulcerated [3]. Figure 1 depicts the histopathology of the excised tumor showing polygonal cells. The low-grade malignant solid tumor had 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] and 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], including necrosis, vascular invasion, perineural invasion [7, 8], and clefts between the tumor and

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stroma [9]. Preauricular lymph nodes may also show reactive hyperplasia [7]. Tumors have increased mitotic activity, that is <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 vary in size, and the cystic spaces present within the lobule are filled with eosinophilic secretion. Stromas show mild-to-moderate infiltration of lymphocytes and eosinophils [7].

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

The primary location of this uncommon malignant intradermal tumor is the head, neck, and trunk regions, and it 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 in 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 is usually poor, and the disease-free survival rate within 5 years is <30%, according to the literature. Therefore, early detection and diagnosis, surgical treatment with wide excision, and Mohs micrographic surgery are recommended for a favorable prognosis.

Metastasis

Because these tumors are histologically malignant, they have high metastatic potential [10], are known for their local recurrence [11], and have a higher incidence of regional and distant metastasis to the surrounding lymph nodes or to other distant sites [4, 12, 13]. The majority of reports suggest that distant metastasis occurs after tumor recurrence and ultimately leads to death.

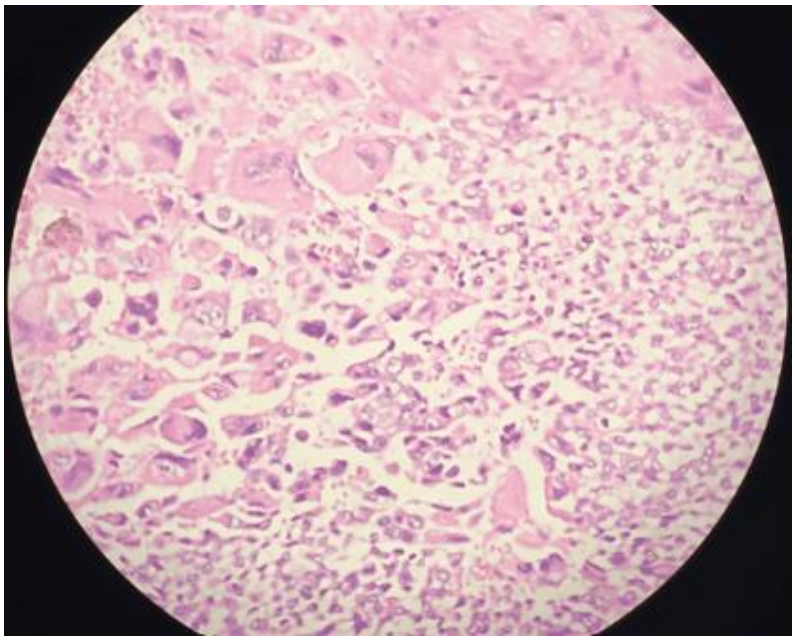

Figure 1. Histopathology of the excised tumor showing polygonal cells.

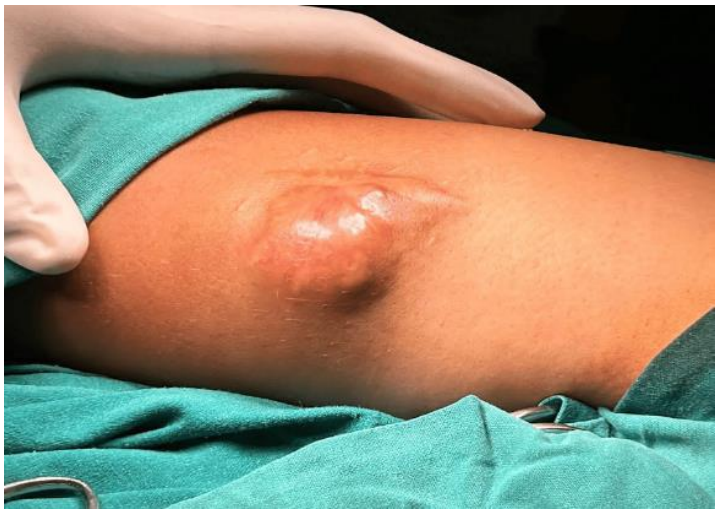

Figure 2. A Clinical presentation of hidradenocarcinoma over the posterolateral aspect of the left arm.

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 tumors are somewhat related to each other. But there are some differences among these tumors as a result of which they are known under different names.

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

The main differences between Hidradenoma and Hidradenocarcinoma are described below.

1. Hidradenoma is an uncommon benign tumor of the sweat gland origin [15]. It is known by different names, including nodular hidradenoma, solid-cystic hidradenoma, poroidhidradenoma, and acrospiroma, whereas hidradenocarcinoma is a malignant form of hidradenoma and is known as Malignant Acrospiroma, Nodular Hidradenocarcinoma, Clear cell Hidradenocarcinoma, Malignant Nodular Hidradenoma, Malignant Clear Cell Hidradenoma, clear cell eccrine carcinoma, or sweat gland tumor [16].
2. Malignant Hidradenoma differs from benign hidradenoma because of the following histological features: 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 and has an asymmetrical growth pattern [18].
4. In hidradenoma tumor cells, a t(11;19)(q14–q21;p13–p12) translocation occurs due to fusion of the mucoepidermoid carcinoma translocated 1 (METC1) gene and mastermind-like 2 (MAML2) gene, but in hidradenocarcinomas, mutations of the TP53 gene and Her2/neu gene amplification occur [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 owing 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].

Fluorescence in situ hybridization (FISH) was 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 a point or non-sense mutation in the exon region of the gene. One 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 led to the 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 a positive immunohistochemical reaction for p53. Lower positivity levels of p53 do not correlate with tumor grade (i.e., whether it is of low or high grade). A case report described a high-grade tumor that showed a negative immunohistochemical reaction [20].

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

Immunohistochemistry

Morphological assessment is of great importance for skin adnexal lesions. Therefore, 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 the help of certain markers [22].

Hidradenocarcinoma shows strong positivity for epithelial markers (10) such as cytokeratin 5/6 (7), cytokeratin 7 (CK7), Epithelial Membrane Antigen (EMA), Carcinoembryonic Antigen (CEA), CAM 5.2, and CAM 19 [9], and may show positivity for p63, Vimentin, GCDFP-15 and negative results for the S100 protein. 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, which helps in identifying the proliferative index and in differentiating between benign and potentially malignant tumors [24].
- p53 is a tumor suppressor gene, but sometimes because of ultraviolet rays there is overexpression of wild type p53 gene or mutation in p53 because of this mutation, an unstable protein product is released, which is detected immunohistochemically. Therefore, 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 differentiates between Hidradenoma and Hidradenocarcinoma [24].
- Bcl-2 can also be used as a marker, as it is an anti-apoptotic protein present on the outer membrane of mitochondria. This protein inhibits programmed cell death. Bcl-2 may stain positively [24].

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

The immunohistochemical markers produce various proteins, and these proteins are immunostained and various tests are used to determine the extent of expression of these immunostained proteins. The example-HercepTest is used for interpreting the extent of expression of the c-erb-2 protein, which is 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, 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]**,** who had exophthalmos for 8 months, and his left eye's vision decreased for 1 month. Visual field defects, reduced vision (0.2), and raised intraocular pressure (20 mmHg) were discovered during an ophthalmological examination of the left eye. Computed tomography (CT) revealed a well-enhancing tumor in the left orbit, with focal bone loss in 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). Focal bone destruction is observed in the lateral orbital walls. Mass spread over the temporalis muscle, superior orbital fissure, and cavernous sinus. They performed a biopsy and discovered that the tumor was a hidradenocarcinoma; as a result, they planned surgical resection with enucleation of the eyeball. The modified lateral supraorbital technique was used to perform complete resection. The tumor appeared hyperemic and yellowish. It was difficult to separate the optic nerve from the tumor. Fat packing and enucleation of the left eyeball were also performed. An instant postoperative MRI revealed no residual tumor. In the dermis, ill-defined multilobular tumors were abundant in a biopsy of the tissue removed by surgery. The tumors were surrounded by a pseudocapsule composed of fibrotic stroma, and there was also a cystic space induced by tumor necrosis. The tumor cells had clear cytoplasm and were round to polygonal in shape. Mitosis and cellular atypia were commonly observed. They also performed an immunohistochemical analysis, which revealed that the tumors were positive for epithelial membrane antigen (EMA), vimentin, cytokeratin, S-100, and high proliferation labeling index (Ki-67 30%), but negative for carcinoembryonic antigen (CEA) and gross cystic disease fluid protein 15 (GCDFP-15). Based on these histological results and imaging examinations, they identified a hidradenocarcinoma on the left upper eyelid extending into the left cavernous sinus with orbital bone damage. 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 fractions was used. The patient's condition was stable for four months, with no recurrences or problems. However, 5 months after the surgery, the patient developed a sudden visual complaint in the right eye. Visual field defects, reduced vision (only light perception), and 16 mmHg intraocular pressure were observed during an ophthalmological examination of the right eye. Focal atrophy in the retina was discovered as a result of the mydriatic test. In addition, the visual evoked potential results showed that the P1 and P3 latencies were delayed, and the electroretinography results showed that rod function was reduced. However, the multifocus electroretinogram was normal, and there was no evidence of recurrence or metastasis on MRI and positron emission tomography (PET)-CT imaging. They hypothesized that visual problems are linked to cancer-related retinopathy (CAR). Systemic steroid therapy and adjuvant chemotherapy were initiated. Cisplatin and 5-fluorouracil were administered. The patient's cognitive ability deteriorated during the first chemotherapy cycle, and cranial nerve palsy (III, IV, and VI) developed. They recommended an MRI examination and a second cycle of chemotherapy; however, the patient refused additional treatment. The patient died 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, and almost 5 years ago, the man resected the tumor from a local clinic, but the mass recurred and increased in size. The tumor was nontender upon palpation. The histology of the tumor indicated that it consisted of irregularly shaped solid sheets and infiltrative clusters of different sizes. The tumor surface had ulcers and multifocal ischemic necrosis. In general, two types of cancer cells were observed: the first type of cells had clear cytoplasm and distinct cell membranes, the nucleus was moderately pleomorphic in nature with vesicular chromatin distribution, and prominent nucleoli were observed. Another type of tumor cell had a basaloid appearance along with scanty eosinophilic cytoplasm and small round ductal structures. Physical examination was conducted to check whether there was any case of regional metastasis and no associated case of cubital or axillary lymphadenopathy. No case of distant metastasis was detected on positron emission tomography-CT (PET-CT). On immunohistochemical staining, the tumor cells reacted positively for p63, CK5/6, and 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 the tumor was a 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 rare case of hidradenocarcinoma within the penis [26]. We report the case of a 46-year-old man. He had lumps of cysts on the shaft of his penis. The patient had no medical history. Upon inspection, a mobile nodule measuring 8 mm in diameter was found over the left side of the distal shaft of the penis, proximal to the coronal sulcus near the frenulum. No palpable lymph were observed. Further wide local excision was performed. A multinodular, solid-cystic, and poorly differentiated carcinoma measuring 15 × 10 mm with a border of less than 5 mm was discovered on histological analysis within the dermis. Upon closer inspection, the tumor resembled a high-grade and malignant cutaneous adnexal tumor of the hidradenocarcinoma subtype. Large lobulated islands of basaloid cells, abundant mitotic figures, and several foci of necrosis were present. Perineal invasion was not observed; however, lymphovascular invasion was observed. The tumor cells stained strongly for p16, p63, s100, MIB-1, and MNF-116 on immunohistochemical analysis, with weaker staining for 34E12 and sparsely 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 that were 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 experienced local recurrence two years later, which was treated with 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 previous condition. Vascular invasion and resection margins were also observed. The results of a subsequent bilateral radical groin node dissection were negative for the disease, but he experienced recurrence in the penile stump a year later. The patient underwent a total penectomy and perineal urethrostomy. Histological investigation of the left side of the corpus cavernosum revealed a single well-circumscribed focus of poorly differentiated adenocarcinoma. He had small lung metastases two months later, which were not observed earlier. He then experienced left inguinal node recurrence 18 months later, which was further removed. The patient's left groin and lungs were treated with radiotherapy (RT). Histological evaluation revealed a lesion compatible with the patient's past condition. Finally, irradiation was performed to treat right tibial metastasis.

Case 4

Singh et al. reported the first case of hidradenocarcinoma in the buttock region, in which a painless mass was found on the left buttock of a 61-year-old woman [4], which has been present for many years but has increased in size over the past 6 months. The mass was violaceous, fungating, and non-tender to palpation. Histological examination revealed a low-grade malignant adnexal tumor with negative

margins. Examination was conducted to determine whether there was any regional metastasis, and upon examination, no associated inguinal lymphadenopathy was detected. Positron emission tomography and computed tomography revealed no evidence of distant metastasis, and computed tomography (CT) scan and biopsy indicated that the mass in the left upper buttock area was associated with feeding vessels. Immunohistochemistry showed positive staining for estrogen and progesterone receptors 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 Nodular Hidradenocarcinoma on the Scalp of a 27-year-old woman [27], who was diagnosed with a nodular lesion for 10 months. The patient had visited 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. The patient was referred to the hospital for removal. 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. The patient had no medical or family history. A CT scan of the occipital region revealed homogeneous low-density tumors covered with skin, but no indication of metastatic illness. Under local anesthesia, the tumor was removed and the skin was closed with a primary suture. The tumor appeared pale and small firm under the microscope, resembling a lymph node. When viewed under the microscope, the lesion appeared 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 skin, and many different-sized cystic cavities in the tumor nodules were present as a result of tumor necrosis. The tumor cells had a lobulated growth pattern with tubular differentiation, monomorphic hyperchromatic nuclei, and a scarcely visible cytoplasm. A pseudocapsule developed around the desmoplastic stroma. Cellular atypia and mitotic figures were also common. The diagnosis of nodular hidradenocarcinoma was confirmed by a final pathological study. No further metastasis was observed. A 1.5-cm radial cutaneous margin was created around the prior scar. A rotating flap is used to close the defect. The surgical wound quickly recovered. Adjuvant therapy was not administered. The patient was well twenty-four months after 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] who had a retroauricular skin nodule on his right side for the last 4 months. The nodule had rapidly increased in size. Biopsy was done and Histopathological examination was performed, immunohistochemical staining was performed, and the tumor stained positively for cytokeratin, and pathological examination confirmed the presence of Hidradenocarcinoma. The tumor was at the T2N0M0 stage, which meant that the primary tumor had 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. Two months later, the patient was diagnosed with metastatic cervical and right submandibular lymph nodes, and skin examination revealed recurrence of the tumor at the primary site. Patient treatment was started, deep cervical and submandibular lymph node dissection was performed, and adjuvant radiotherapy was planned. While the treatment was ongoing, the patient was lost to follow-up for 4 months, after which the patient started attending the emergency department along with disturbed consciousness due to cavernous sinus thrombosis. However, 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], in which a 73-year-old Caucasian male reported to the emergency room with progressive dyspnea over an 8-weeks period accompanying by chest pain on exertion. He also had 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. The patient was a former smoker with no prior medical history. The patient was clinically diagnosed with anemia, heart failure, and 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 multiple active bleeding spots. There was no swelling of the lymph nodes in the neck, and his cranial nerves were healthy. His complete blood count revealed 5.7 g/dl hemoglobin, leukocytosis, and abnormal liver function test results. 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 biopsy of the neck lesion. No metastases were found on abdominal ultrasound. A computed tomography (CT) scan of his chest and abdomen revealed a 1.5 cm lesion at the base of the left lung. According to CT-guided biopsy, the lung lesion had modest atypia with no conclusive cancer cells. The lump was superficial and lateral to the sternocleidomastoid muscle on MRI examination of the neck. Surgery was determined to be the optimal treatment after consultation with a multidisciplinary team of head and neck oncologists. The patient underwent total removal of the lesion and repair using 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. The patient was administered adjuvant radiotherapy to reduce the likelihood of local recurrence. A subsequent chest CT scan revealed that the lesion in the lung had decreased in size, indicating the presence of inflammation. There was no sign of locoregional recurrence two years after surgery, and the aesthetic appearance was outstanding.

Case 8

Son et al. reported a case in which a thickened nail bed was present on the left index finger of a 76-year-old woman, and it had a darkish discoloration that gradually increased [30, 31], with 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, it was initially 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. A second partial biopsy was performed under the influence of local anesthesia, and histopathological examination of the sample showed that the lesion was a poorly circumscribed intradermal nodule with infiltrative growth. The tumor cells had a morphology similar to that of nodular hidradenomas. The tumor cells were highly atypical and had small lobules, nests, cords, and partial cystic portions. The tumor cells had nuclear hyperchromatism, prominent nucleoli, and abundant clear cytoplasm with no vascular or perineural invasion, and the tumor cells reported a slight increase in mitotic activity. Immunohistochemistry revealed that the tumor cells strongly stained positive for p63 and focally 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 proliferation index was 3%. All pathological analyses confirmed that it was a case of hidradenocarcinoma. Physical examination was conducted to check for regional metastasis, and radiological examinations like PET –CT were conducted to check for distant metastasis, and no case of metastasis was detected. Surgery was performed, the tumor was completely excised under local anesthesia, and no cases of local recurrence or distant metastasis were 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 sweat glands. The cases span a wide range of anatomical locations, including the orbit, hand, penis, buttock, scalp, neck, and fingers. 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. 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, whereas others remained disease-free after treatment. These cases highlight the importance of early diagnosis, accurate histopathological evaluation, and individualized treatment planning for the management of hidradenocarcinomas.

Treatment

To date, there are no established treatment options for the management of hidradenocarcinoma, 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 the treatment of choice. After diagnosis, wide surgical excision should be performed as soon as possible as the tumor is known to recur locally and metastasize to the 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 for rapid progression following trauma, any nodular lesion suggestive of HDC measuring less than 2.5 cm should be treated by biopsy resection 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].

Furthermore, different types of surgery include classical cancer surgery, two-step surgery, which may provide better margin control, and Mohs micrographic surgery, through which excellent control can be achieved [25]. Mohs micrographic surgery (MMS) with or without wide local excision is the preferred standard treatment for 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 preserving the greatest 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 cases where surgery is impossible, additional treatment options such as adjuvant therapies (radiation and chemotherapy) should be considered, especially in cases 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. Various chemotherapy regimens include first-line chemotherapy; 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 combination with radiotherapy, as studies have shown that disease progression occurs even after this treatment [25].

In addition, combined treatment with wide excision and adjuvant radiotherapy is considered appropriate [5]. Electrochemotherapy (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) and cellular membrane electroporation. With the help of electroporation, chemotherapeutic drugs penetrate the cytoplasm, which leads to higher levels of cytotoxicity in cancer cells with fewer adverse effects. ECT is a non-thermal, safe, and well-tolerated therapeutic 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 synergistically with RT or a combination of ECT, RT, and systemic chemotherapy. External RT in conjunction with ECT-bleomycin was first described in humans by the Hellenic Group of Electrochemotherapies. As a result, combination therapy with ECT and RT can provide outstanding therapeutic results for all forms of skin malignancies in the head and neck area [25].

Further targeted therapies, such as trastuzumab, are effective for the management of metastatic hidradenocarcinomas. Other targeted therapies include Akt/PI3K/mTOR pathway inhibitors and hormonal agents, such as androgens [25].

However, 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 results and the patient's quality of life. In addition, patients should be monitored monthly. With each follow-up, patients should be checked for local recurrence, radiation toxicity, and metastatic spread. In cases of clinical suspicion, radiological examinations, including radiography, PET scans, and CT scans, may be considered [25].

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

CONCLUSION

In conclusion, hidradenocarcinoma (HAC) is an aggressive malignant tumor derived from the intradermal duct of the 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 is often diagnosed late because of its insidious growth pattern.

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

The treatment options for HAC are limited, with wide surgical excision being the preferred option. Mohs micrographic surgery is recommended for its high cure rate and ability to preserve the 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 the treatment outcomes and prognosis. Early detection and diagnosis are crucial for a favorable prognosis, and patients should be closely monitored for local recurrence and metastatic spread.

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