Hidradenocarcinoma of the temporal area successfully treated with concomitant electrochemotherapy and radiotherapy

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Abstract
Hidradenocarcinoma, the malignant counterpart of hidradenoma, is an extremely rare malignant tumour, which may exhibit an aggressive clinical course. The standard primary treatment is wide local excision with or without lymph node dissection. Radiotherapy has also been used in some cases but with controversial outcomes. At the University of Thessaly—Faculty of Medicine and the University Hospital of Larissa, Greece, we successfully treated a hidradenocarcinoma of the skin of the tempo-parietal area using a combination of electrochemotherapy and radiotherapy.

Introduction
Hidradenocarcinoma (HADCA), the malignant counterpart of hidradenoma, is an extremely rare malignant tumour, which may exhibit an aggressive clinical course with metastasis and/or local recurrence1. A very limited number of cases have been reported in the literature and the nomenclature has been inconsistent, making evaluation of clinical data more difficult. The standard primary treatment is wide local excision with or without lymph node dissection. Radiotherapy (RT) has been used in some cases of HADCA with inconsistent results. Regardless of the surgical management technique, HADCA may follow an aggressive course, demonstrating local recurrence rates of up to 50%, metastasis rates of 60% and a 5-year disease-free survival rate <30%. Faster growth and invasion of the surrounding tissues are characteristics of their biological behaviour after each local relapse2. They may also metastasize widely (at a rate of 60%), into regional nodes, bone, viscera and skin and cause death. HADCAs may follow an aggressive behaviour after each local relapse2.

Case study
An 86-year-old woman presented at our hospital complaining of a painless mass in the skin of the right temporo-parietal area that had progressively increased in size during the previous months. There was no history of trauma to the area and the patient denied suffering any pain or paraesthesia associated with the lesion, although she mentioned an episode of bleeding. On physical examination, the patient had a 48 × 45 × 18 mm sharply circumscribed solitary lesion not fixed to the underlying tissues and with normal overlying skin. Gross examination of the biopsic specimen showed a circumscribed solid mass measuring 27 × 20 × 11 mm and partly covered by skin. A multinodular growth pattern with a few small dispersed cystic areas was observed in the cut section.

Histopathological examination showed several tumour nodules varying in size and shape involving the dermis and exhibiting an infiltrative growth pattern in some areas. There was no connection with the epidermis. The nodules consisted of round-to-polygonal epithelial cells with distinct cell borders, clear to eosinophilic cytoplasm and pleomorphic nuclei, with frequent mitotic figures (Figure 1). Several central areas of necrosis were observed. Evidence of ductal differentiation was detected focally in the form of small round ducts and intracytoplasmic vacuoles (Figure 1). Hyalinized fibrous tissue and focal myxoid degeneration was widespread between tumour cell nests. Extensive sectioning did not reveal vascular or perineural invasion. The lesion extended close to the deep excisional margin.

Immunohistochemical staining showed positivity for AE1/AE3, p63 and focal positivity for carcinoembryonic antigen (CEA) at the luminal border of ductal structures. Stains for Melan A, HMB45, TTF-1, ER and CD-10 were negative. In some areas, Ki-67 was positive in >90% of tumour cells. Periodic acid-Schiff staining demonstrated the presence of glycinogen in several tumour cells.

The findings were suggestive of a malignant adnexal skin tumour, more consistent with clear-cell HADCA. The staging procedure with skull base, neck and chest computed tomography (CT) scans was negative for evidence of metastatic disease, and the patient was referred to a multidisciplinary meeting to resolve the therapeutic challenge and deal with the therapeutic decision.

In our case, a major surgical procedure was contraindicated because of the patient’s old age and poor performance status. For the same reasons, a combined treatment with RT plus intravenous chemotherapy seemed impossible. Moreover, based on the literature, which offers limited and contradictory data, there was little to...
After discussing the case at a multidisciplinary meeting, it was decided that given the patient’s age and poor performance status, the only possible treatment would be combined concurrent RT and electrochemotherapy (ECT) to maximize the likelihood of complete local control. Thus, the patient underwent a single session of ECT with intravenous bleomycin (15000 IU/m² or 15 ml/m² of body surface) and seven sessions of accelerated hypofractionated RT. With a direct electron-beam field of 10 MeV energy and a dose/fraction of 6 Gy administered twice a week for a total of 7 fractions, the lesion received a total dose of 42 Gy over a total period of 22 days (equivalent radiation dose: 71 Gy).

Results

A monthly clinical follow-up on an outpatient basis showed that the results of the combined therapy had been excellent. Strikingly, there was complete remission of the lesion, as can be seen from Figures 2 to 4. Quarterly monitoring with head-and-neck and chest CT scans was negative for evidence of metastatic disease.

Discussion and conclusion

HADCAs represent only a small group of adnexal neoplasms but may pose diagnostic problems, both clinically and pathologically. Lesions present most commonly on the face or extremities, although they may appear anywhere on the body surface, arising de novo or sometimes associated with a pre-existing hidradenoma. They may be present as slowly expanding masses without any specific symptoms or clinical presentation suspicious for malignancy, leading to delayed diagnosis.

The histopathological diagnosis of HADCAs may be problematic due to a combination of factors, including the rarity of the neoplasm, variable morphology and inconsistent nomenclature and classification. This is reflected in the variety of names which have been used to describe this type of neoplasm.
tumour. The histopathological distinction of such tumours from lesions characterized as atypical hidradenomas is based on an infiltrative growth pattern, deep extension, necrosis, nuclear pleomorphism and an increased number of mitoses. Some HADCAs lack nuclear atypia and their diagnosis is based on architectural characteristics.

HADCAs may contain several types of cells, including clear cells with abundant glycogen, squamoid cells and transitional form with focal formation of tubular and ductal structures. When making the diagnosis, it is essential to exclude, in particular, other appendageal skin tumours with eccrine and apocrine differentiation, especially those presenting with clear cell cytology, clear cell squamous cell carcinoma and balloon cell melanoma. In comparison to benign nodular hidradenomas, HADCAs are larger, asymmetrical in their configuration and show evidence of invasion into the surrounding tissue. HADCAs may also occasionally mimic metastatic adenocarcinomas.

Immunohistochemistry can be useful in these rare cases, since positivity for p63 has been reported to support a diagnosis of primary malignancy. Clear cell carcinomas of thyroid or pulmonary origin may be excluded by TTF-1 staining. The absence of prominent vasculature and immunohistochemical stains may help in excluding metastatic clear-cell carcinoma of renal origin.

RT has been used in several cases of HADCAs with conflicting results; in some reports RT appeared to be effective, while in others, radio-resistance was observed. Regarding combined radiochemotherapy, some authors have concluded that adjuvant chemotherapy and RT have no impact on local control or survival.

ECT is a recent treatment for cancer involving a combination of locoregional or intravenous administration of very low doses of an antineoplastic drug (usually bleomycin or cisplatin) with electroporation of the cellular membranes. The cancer cells are exposed to short/high electric field pulses (with a duration of micro- to milliseconds) delivered by an electroporator. This causes reversible permeabilization of cell membranes, thereby improving penetration of chemotherapeutic or doxyribonucleic acid plasmids into the cytoplasm. The result is endogenous local amplification of the effects of the antineoplastic agent, with high levels of cytotoxicity in cancer cells, which usually demonstrate low or possibly even zero membrane permeability when such an agent is used. There are few side effects when this method is used, and normal function of neighbouring organs and surrounding healthy tissue is maintained. As a result, the patient tolerates the therapy well and recovers rapidly. This is true even for areas of the body which have already been subjected to chemotherapy and/or RT. For all forms of solid tumours, ECT offers a non-thermal, safe, well-tolerated treatment method suitable mainly for cutaneous and subcutaneous areas.

The clinical use of ECT was pioneered by Mir et al. (beginning in 1990 at the Institute Gustave Roussy, Paris, France—bleomycin using ECT) and by Sersa et al. (since 1994 at the Institute of Oncology, Ljubljana, Slovenia—cisplatin using ECT). International medical literature now includes more than 400 records of the clinical use of ECT. These contain details of the treatment of more than 1500 patients all over the world.

It is well known that the effects of RT on human tumours are boosted by traditional intravenous chemotherapy. ECT also acts synergistically with RT on its own or when a combination of ECT plus RT plus systemic chemotherapy is used, as reported by Kranjci et al. and Shil et al. in preclinical studies. In animal models, very good results have also been obtained from radiosensitizing ECT with the use of bleomycin, cisplatin or doxorubicin. To the best of our knowledge, the Hellenic Group of Electrochemotherapy was the first to report the use of external RT combined with ECT-bleomycin in humans. In conclusion, we believe that for all types of skin tumours in the head and neck area, combined therapy of concomitant ECT and RT can be of excellent therapeutic outcome, while cosmesis and function of the healthy surrounding tissues can be safely preserved.

References
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