Keratoacanthoma-like nodules as first manifestation of metastatic epithelioid trophoblastic tumor

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Abstract

Cutaneous metastases are rarely the initial manifestation of a previously undiagnosed malignancy and keratoacanthoma-like lesions are a notoriously unusual presentation pattern of cutaneous dissemination of a primary tumor. Herein, we report a 40-year-old woman presenting to our dermatology department with multiple keratoacanthoma-like scalp nodules. Subsequent investigation determined it to be the first manifestation of a disseminated endometrial epithelioid trophoblastic tumor, eventually causing the patient's death. Epithelioid trophoblastic tumor, a rare form of gestational trophoblastic disease, is a recently described neoplasm whose cutaneous metastasis has not been previously reported in the literature.

Keywords: epithelioid trophoblastic tumor, cutaneous metastases, keratoacanthoma

Introduction

Gestational trophoblastic disease (GTD) represents a spectrum of interrelated placental trophoblastic lesions, which can be further classified into benign and malignant [1, 2]. Epithelioid trophoblastic tumor (ETT), first described in 1998 [3], is the most recent addition to GTD. With approximately 100 cases reported until recently [4], it is a form of GTD arising from chorionic-type intermediate trophoblastic cells [2, 5]. Although metastasis is known to occur in ETT, cutaneous metastases have not been previously reported. We present the case of a reproductive-aged woman with an undiagnosed ETT, first manifesting with keratoacanthoma-like cutaneous metastases.

Case Synopsis

A 40-year-old woman, with no relevant medical history, presented with multiple nodules on the scalp. The patient stated the first lesion, in the right frontal region, appeared 8 months before and spontaneously regressed over two months. After that, several similar persistent nodules developed, scattered across the scalp; they had rapidly grown over a few weeks.

On physical examination there were 10 firm, dome-shaped, well-circumscribed nodules with central crateriform ulceration and hyperkeratotic cores, ranging in size from one to 6cm (**Figure 1**). Enlarged cervical lymphadenopathy was appreciated. The patient denied accompanying systemic symptomatology.

A skin biopsy of one of the nodules revealed anastomosing cords and nests of atypical epithelioid cells with eosinophilic cytoplasm and large, pleomorphic nuclei (**Figure 2**). Immunohisto-

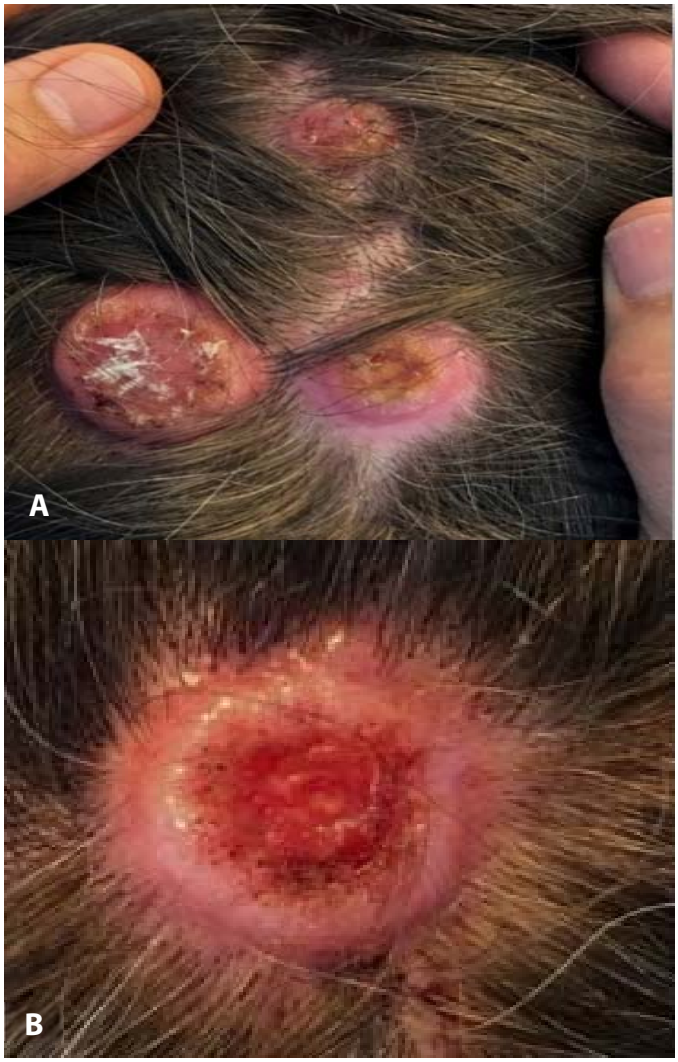

Figure 1. ***A)*** *Examination revealed well-circumscribed nodules resembling keratoacanthomas.* ***B)*** *Detail of one of the nodules, with central crateriform ulceration and hyperkeratotic core.*

chemical staining showed diffuse positivity for cytokeratin 5/6, 34BE12 and focal positivity for epithelial membrane antigen (EMA). In contrast to the clinical impression, the histological features of the lesions were not compatible with keratoacanthoma. The conclusion pointed to a fragment of poorly differentiated carcinoma; considering the multifocality of the lesions and the limited connection with the epidermis, the hypothesis of metastasis was favored.

Within a few weeks the patient reported the onset of persistent cough, pain of the left shoulder and upper limb, intermittent vaginal bleeding, and the presence of a vulvar mass. The patient was then evaluated by the gynecology department. Previous reproductive history included a spontaneous abortion and 2 cesarean deliveries, the last one 9 years before. On examination there was a solitary nodule on the inner side of the right labium majus, measuring 3cm in diameter and macroscopically similar to the lesions on the scalp. The biopsy of the vulvar nodule revealed morphological features identical to those of the scalp biopsy, but this time immunohistochemical staining identified positivity for beta-human chorionic gonadotropin (β-HCG), raising the possibility of metastasis of an epithelial malignant neoplasm producer of β-HCG. Subsequent imaging performed disclosed an irregular endometrial surface with an expansive tumor with irregular borders, locally infiltrating the myometrium. These findings pointed to a diagnosis of endometrial ETT. Serum level of β-HCG was determined, showing high levels (449mIU/mL) that gradually increased in subsequent evaluations (556, 924, 1187mIU/mL). The workup included endoscopic studies showing an ulcerated tumor in the descending colon; biopsy revealed morphological findings similar to those of the other histological studies. Histological examinations of the cutaneous, vulvar, and intestinal material were reviewed and all lesions exhibited the same histopathological and immunohistochemical findings, consistent with the diagnosis of ETT.

A battery of radiological studies was performed, revealing multiple systemic metastases: nodal, pulmonary, pleural, cardiac (left ventricular), hepatic, pancreatic, osseous, renal, intestinal, vaginal (labia majora), muscular, subcutaneous, and cutaneous. At

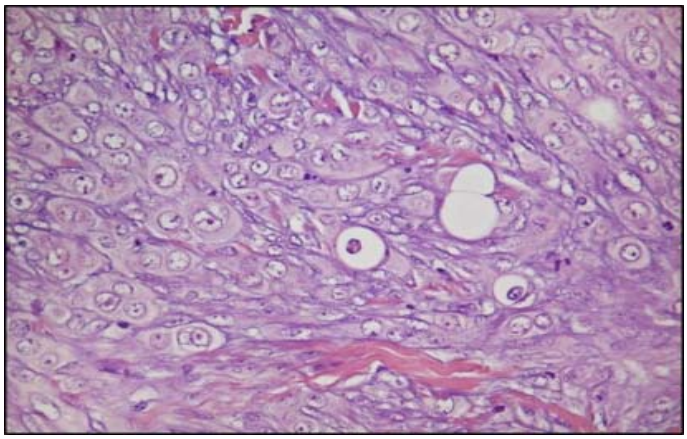

Figure 2. *Histologic examination revealed atypical epithelioid cells with eosinophilic cytoplasm and large and pleomorphic nuclei. H&E, 400×.*

this point, the patient was diagnosed as having metastatic ETT. Multi-agent chemotherapy (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) was initiated but had to be suspended owing to medical complications. A palliative approach, with supportive care and palliative radiation therapy was advocated. However, the patient deteriorated rapidly and died approximately 7 months after first presenting to the dermatology department.

Case Discussion

Epithelioid trophoblastic tumor is an exceedingly rare tumor, seen mostly in reproductive-aged women [6]; it can be a sequel of any gestational event. Approximately one-third of cases arise following a spontaneous abortion or hydatidiform mole, whereas the majority occur after a full-term pregnancy [2, 5, 7]. The average interval from the antecedent gestational event to presentation varies, ranging from two months to as long as 18 years [2, 4, 5]. Epithelioid trophoblastic tumor can present in both intrauterine and extrauterine sites [2, 6]. Most often the uterus is the primary site (40%), followed by the cervix (31%). The lung is the most common extrauterine site, accounting for 19% of cases [2]. The most common presentation is with abnormal vaginal bleeding, although the presentation in some cases relates to metastases in lung, vagina, or broad ligament [2, 5, 6, 8]. At the time of diagnosis, serum β-HCG levels are elevated but generally do not exceed 2500mIU/mL [2, 4-6, 8].

The diagnosis can usually be made on morphological grounds. In particular suspicion should be high because the patients are usually relatively young, have experienced a gestational event, and exhibit an elevated serum β-HCG [8]. Microscopically the tumor presents features resembling a poorly differentiated carcinoma. The neoplastic cells are small and epithelioid, with eosinophilic-to-clear cytoplasm. The cells are arranged in a monomorphic pattern of nests and cords, embedded in a hyaline matrix [4, 5, 8]. Although the immunohistochemical staining patterns of the reported cases are not uniform [8], inhibin alfa, cytokeratin AE1/AE3, EMA, and other trophoblastic markers including β-HCG, human placental lactogen (HPL), and placental alkaline phosphatase are commonly expressed [2, 5].

Although ETT displays an unpredictable but usually benign and indolent behavior in most instances [1, 5, 6], metastases and death occur in approximately 25% and 10% of patients, respectively [6, 8]. Epithelioid trophoblastic tumor is relatively chemotherapy resistant and surgical resection is the primary treatment modality [2]. The differential diagnosis of ETT includes other forms of GTD (placental site nodule, exaggerated placental site reaction, placental site trophoblastic tumor, and choriocarcinoma), squamous cell carcinoma of the cervix, and epithelioid leiomyosarcoma [2, 6, 8]. Placental site trophoblastic tumor (PSTT) can be difficult to differentiate from ETT as these are both malignant neoplasms of subtypes of intermediate trophoblast [8]. Histologically, ETT is distinguished from PSTT by its smaller, more monomorphic cells and by its nested, nodular, well circumscribed growth pattern, unlike the sheet-like deeply infiltrative pattern and prominent vascular invasion seen with PSTT [6, 8, 9]. Relatively to ETT, PSTT cells display a characteristic immunostaining pattern, with a more diffusely positive staining for HPL and only focal staining for β-HCG [2, 6,9-11]. The morphological features, along with the scantly infiltrative pattern and the absence of staining for HPL, favored the diagnosis of ETT, as opposed to previously reported cases of scalp metastasis of PSTT [10, 11].

Cutaneous metastases are markers of a poor prognosis, correlating with disease progression and a median survival time after their presentation of approximately 3-6 months [12-14]. Clinical presentation of cutaneous metastases is variable. Typically manifesting as dermal and subcutaneous papules and nodules, they can also mimic dermatologic conditions such as alopecia, cutaneous horn, cysts, dermatitis, bacterial (such as erysipelas and acute paronychia) and viral (such as zosteriform lesions) infections, or vascular lesions (such as pyogenic granuloma). Keratoacanthoma-like lesions are much more rare [14-16].

The most common metastatic sites for GTD are the lungs, liver, and brain. Gestational trophoblastic

disease with skin metastases has been reported but is exceedingly rare [17, 18]. It is reported that ETT can metastasize to the lung as well as to the brain, liver, abdominal cavity, vagina, tonsil, and lymph nodes [6, 8]. However, to the best of our knowledge, there are no previous reports of ETT with cutaneous metastases.

Cutaneous metastases of internal malignancies with keratoacanthoma‐like morphology are extremely rare [14], with fewer than 20 cases reported until now [12]. Lung, larynx, breast, esophagus, bronchus and renal cancer, mesothelioma, angiosarcoma, chondrosarcoma, anaplastic large cell lymphoma, and malignant melanoma are the primary malignancies accounting for the majority of these reports [12-14,19]. In the reported cases, keratoacanthoma-like cutaneous metastases tend to have a biologic behavior and appearance similar to that of an idiopathic keratoacanthoma: a solitary, asymptomatic, rapidly growing, firm, dome-shaped nodule with a central keratin-filled crater that grows rapidly in 4-to-6 weeks and spontaneously involutes within 6 months [15]. When multiple, the lesions should also be differentiated from previously known conditions of multiple keratoacanthomas, such as Muir-Torre syndrome, generalized eruptive keratoacanthomas of Grzybowski, and Ferguson-Smith type multiple keratoacanthomas [14]. Keratoacanthoma-like cutaneous metastases tend to appear in the course of a previously diagnosed internal malignancy rather than be the first sign of the disease [13]. The histological findings observed in keratoacanthoma-like metastatic lesions are generally similar to those in the primary site tumor [12, 14, 15].

Conclusion

In summary, we present a patient with metastatic ETT, a rare primary tumor whose usual first manifestation is abnormal vaginal bleeding. However, our patient presented with multiple cutaneous metastases. Although vaginal and colonic metastases have been previously described [8], to the best of our knowledge this is the first report of ETT with cutaneous metastases. The morphologic pattern of keratoacanthoma-like metastases is also notable. The spontaneous regression of the first lesion the patient reported is consistent with the expectable evolution of the lesions, similar to idiopathic keratoacanthomas. However, the disseminated metastases, including the uncommon left ventricular tumors, are remarkable since ETT is considered a relatively indolent tumor. Although rarely encountered, multiple keratoacanthoma-like nodules should raise the possibility of cutaneous metastases of an internal malignancy.

Potential conflicts of interest

The authors declare no conflicts of interests.

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