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Epithelioid Trophoblastic Tumor: Case Report

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Abstract

Introduction: Epithelioid trophoblastic tumor (ETT) is a distinctive but very rare gestational trophoblastic tumor. Patients diagnosed with this disease usually are of the reproductive age group and typically present with abnormal vaginal bleeding. **Presentation of case**: This report details a case of a 47-year-old premenopausal female, who was diagnosed with epithelioid trophoblastic tumor and underwent subtotal abdominal hysterectomy with bilateral salpingectomy. The patient has signed a formal consent that authorized the publication of her case. **Discussion**: Through this report we will be discussing epithelioid trophoblastic tumor (ETT) along with its morphology and immunochemical breakdown. Discussion will involve its prognostic factors and treatment modalities. **Conclusion**: Although it's not confirmed, ETT is said to be mostly chemo resistant, and thus hysterectomy is still the mainstay of treatment. Because of its rarity, limited data have been published regarding follow-up and surveillance for recurrence.

Keywords

Epithelioid Trophoblastic Tumor (ETT), Gestational Trophoblastic Disease (GTD), Choriocarcinoma (CC), Outcome

1. Introduction

Gestational trophoblastic disease (GTD) is known to be an abnormal proliferation of placental trophoblasts and is divided into benign and malignant neoplasms. Benign neoplasms include placental site nodules, exaggerated placental site, and hydatidiform moles. Whereas the malignant neoplasms are known as gestational trophoblastic neoplasia, include choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT), and invasive moles that do not spontaneously resolve [1]. Epithelioid trophoblastic tumor (ETT), an unusual type of trophoblastic tumor in which its growth pattern mimics squamous-cell carcinoma, has only recently been described [2] [3]. ETT is a rare dis-

ease with an incidence of 0.2 to 0.5 cases per 100,00 women of child-bearing age.

The histological characteristics of ETT were first reported by Mazur in 1989 under the term "atypical CC" [4]. However, Shih and Kumar then used the term epithelioid trophoblastic tumor (ETT) to describe the neoplasms composed of chorionic-type intermediate-trophoblast cells (ITCs) [2].

Epithelioid trophoblastic tumor (ETT) is an exceptionally rare form of gestational trophoblastic neoplasia (GTN), accounting for approximately 1 - 2% of all GTN cases. Due to its rarity, precise global incidence rates are not well-established. In Japan, a study reported an incidence of 0.07 per 100,000 live births. Since its initial description in 1998, around 110 cases have been documented in the literature. Given its low incidence, comprehensive global data are limited, and much of the current understanding is derived from individual case reports and small case series.

Given the global scarcity of reported cases, it is plausible that ETT is exceedingly rare or underreported in Bahrain. In this paper, we will present a case of ETT, which to our knowledge is one of the first cases to be reported in the Kingdom of Bahrain.

2. Case Presentation

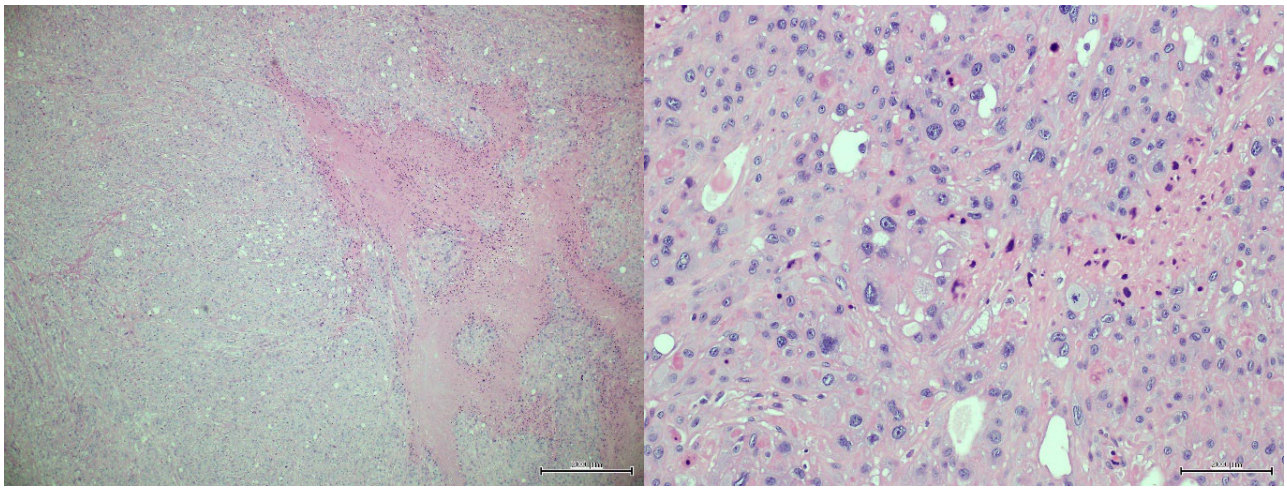
A 47-year-old female (para 2, previous 2 cesarean sections), known case of asthma, dyslipidemia and type 2 diabetes mellitus, presented initially to the emergency room complaining of prolonged menses associated with abdominal pain. According to the patient her menses prior to presentation were regular and of normal flow. Ultrasound scan showed bulky lobulated uterus suspected of hosting multiple hypoechoic fibroids with scattered calcifications. Both ovaries are normal in size, site and shape with no masses or cysts and intact vascularity. No pelvic collection. Investigations were as follows; hemoglobin (12.1 g/dl), BHCG: 17, CA 19-9 and CA 125 were within normal (17.1/7.6) respectively.

Patient was seen in the clinic; pap smear was repeated which came out to be negative. MRI was done and showed intact vascularity of ovaries and enlarged uterus showing large ill-defined outline mass lesion, almost replacing the whole uterine corpus and malignancy could not be excluded. The decision to undergo subtotal hysterectomy with bilateral salpingectomy was then taken based on the above results. The intraoperative findings included bulky uterus with multiple fibroids and friable tissue. An iatrogenic opening was created on the uterus which resulted in drainage of pus from the uterus itself. A right sided ovarian cyst was noted and aspirated. Subtotal hysterectomy and bilateral salpingectomy were done in addition to peritoneal lavage. The tissue was then sent for histopathology.

Histopathology report was positive for epithelioid trophoblastic tumor (pT1). The slides presented below show a tumor that is composed of expansile growth of relatively uniform, medium sized cells arranged in large sheets and nests with extensive necrosis (**Figure 1(A)**) along with moderate nuclear atypia with occasional mitotic figures (**Figure 1(B)**). The tumor involved the cervix, which was detached from the uterine corpus and the procedure was subtotal hysterectomy with bilat-

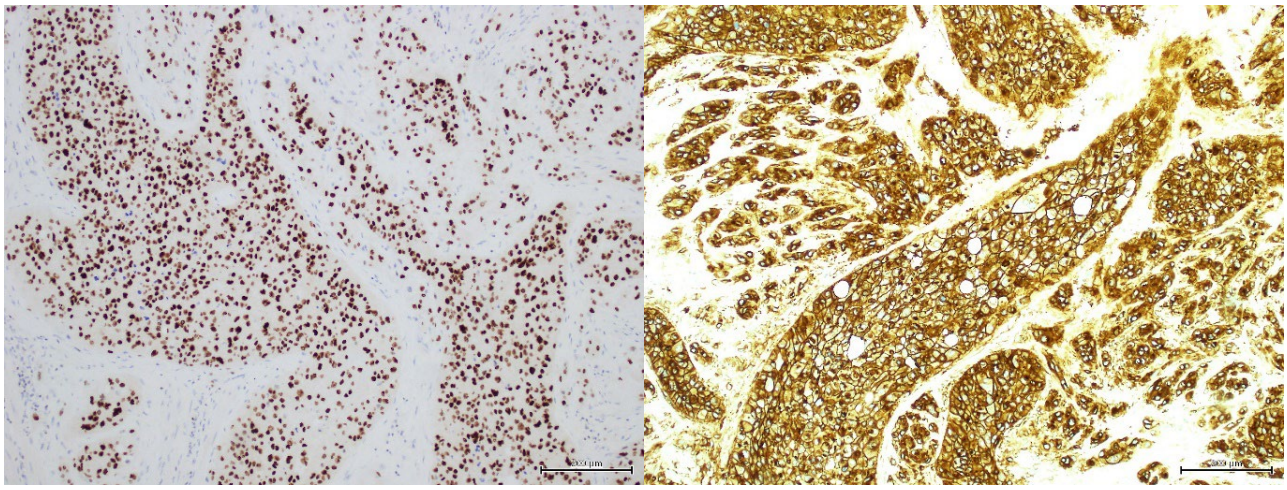
eral salpingectomy. However, the endocervical margin was clear. On further study, the immunohistochemical findings were positive for pan-cytokeratins (AE1/AE3), p63, GATA-3 and CD10 (**Figure 2(A)** and **Figure 2(B)** respectively), while negative for desmin, SMA, ER, PR, cylinD1 and CD56, with the proliferation index by ki67 being 15% - 20%. Involvement of the right and left parametrial margins by the tumor were noted but as mentioned previously the endocervical margin was clear. Other tissue/organ involvement was not found but lymphovascualr invasion was present. The pathologic stage classification (pTNM) was pT1 at least.

The patient was seen in the clinic post-operatively, CT chest was done which showed left lower lobe basal segmental pleural based solid non-calcified nodule measuring 3 × 2.2 cm. PET scan showed post-operative changes and FDG (fluorodeoxyglucose) avid left inguinal lymph nodes of equivocal nature. The case was



(A) (B)

Figure 1. (A) Showing expansile growth of relatively uniform, medium sized cells arranged in large sheets and nests with extensive necrosis. (B) moderate nuclear atypia with occasional mitotic figures.



(A) (B)

Figure 2. (A) Tumor cells showing GATA-3; (B) tumor cells showing CD10.

then discussed in the Kingdom of Bahrain's National Tumor Board and was advised to undergo medical oncology review for adjuvant systemic treatment following the intermediate trophoblastic disease protocol as further surgical intervention was not recommended. Specific mode of treatment post operatively has yet to be discussed with the patient. The diagnosis and staging were updated to be epithelioid trophoblastic tumor of stage pT2 (**Figure 2(A)** and **Figure 2(B)**).

3. Discussion

Epithelioid trophoblastic tumor is a rare tumor and as mentioned earlier it is mostly seen in women in the reproductive age. Although it presents in women between the ages of 18-48 (with the average age being 36.1) [2], some reports have shown that it may affect postmenopausal women as well [5]. The human chorionic gonadotropin hCG in patients with ETT is usually elevated at the time of diagnosis [2]. However, our patient did not fit this criterion as her serum hCG was 17.

Studies show that there is diffuse expression of cytokeratins (AE1/AE3), CK-18, epithelial membrane antigen and p63 in those who are diagnosed with ETT [6]. Both cytokeratines (AE1/AE3) and p63 were noted in the immunohistochemistry of our patient. ETTs are also positive for inhibin-alpha, with positive cells ranging from 20% to 80%. Human placental lactogen (hPL), human chorionic gonadotropin (hCG), and Mel-CAM (CD146) are only focally expressed [7] [8]. Overall, immunohistochemistry aids in differential diagnoses. BHCG and human placental lactogen-positive cells are generally not present in squamous cell carcinoma. Furthermore, unlike the relatively low Ki-67 labeling index of ETTs (10% - 25%), cervical squamous cell carcinomas always have a very high Ki-67 labeling index (>50%) [9]. Association between high mitotic index and more aggressive behavior has been reported [10]. However, in reported cases of ETT with unusually high Ki67 nuclear labeling indices, both patients are alive and well postoperatively though neither patient presented with metastases, and both were treated solely with surgical intervention [1].

Morphologically, epithelioid trophoblastic tumor cells are arranged in nests, cord and masses of cells which are closely associated with an eosinophilic, fibrillar and hyaline-like material [8]. Neoplastic cells typically are small with an epithelioid and eosinophilic cytoplasm [5]. Keratin pearls are said to be found in ETT whereas intracellular bridges are seen in squamous cell carcinoma, this helps us differentiate the two neoplasms from one another [9].

Palmer *et al.* summarizes the treatment modalities in 52 patients diagnosed with ETT. Thirty-nine percent of patients were treated with surgery only (31% underwent total abdominal hysterectomy, 4% had dilation and curettage and the 4% who had lung metastasis underwent resection of the pulmonary mass). In total, surgical intervention included hysterectomy (73%), D&C (19%), lung resection (21%), bowel resection (2%), and wide local excision of vaginal tumor (2%). Four percent of patients underwent radiation therapy. Twenty-nine percent of patients had pre-operative chemotherapy and 48% had chemotherapy post-operatively.

Due to variable regimens, the success rate of chemotherapy is hard to obtain [1] [11]. Surgical resection remains the primary treatment modality [1].

Epithelioid trophoblastic tumor (ETT) is a rare gestational trophoblastic tumor with characteristic histologic and immunohistochemical patterns. Due to its rarity and wide spectrum of clinical presentation, cases such as the one presented often go misdiagnosed which in turn become mismanaged. It is important to note that diagnosis of ETT is primarily made through morphological and immunohistochemical studies. However, ETT can be present in a variety of patients with different backgrounds and does not necessarily follow the common clinic presentation hence its accurate differential diagnosis would properly guide therapy and change prognosis. Therefore, it is critical for physicians to be aware of the distinct presentations [12]-[14].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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