Gynecologic Oncology 137 (2015) 456–461

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Epithelioid trophoblastic tumor: A single institution case series at the New England Trophoblastic Disease Center

M.R. Davis [a,*], B.E. Howitt [d], B.J. Quade [d], C.P. Crum [d], N.S. Horowitz [a,b,c], D.P. Goldstein [a,b,c], R.S. Berkowitz [a,b,c]

[a] Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b] Dana Farber Cancer Institute, Boston, MA, USA
[c] New England Trophoblastic Disease Center, Donald P. Goldstein MD Trophoblastic Tumor Registry, Boston, MA, USA
[d] Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

HIGHLIGHTS

- This series describes the first asymptomatic cases with extrauterine disease.
- Patients with ETT demonstrated resistance to multiple agent chemotherapy.
- Surgical management with hysterectomy improved outcomes in patients with ETT.

ARTICLE INFO

Article history:
Received 30 December 2014
Accepted 4 March 2015
Available online 12 March 2015

Keywords:
Epithelioid trophoblastic tumor
Gestational trophoblastic neoplasia

ABSTRACT

Objective. Epithelioid trophoblastic tumor (ETT) is a rare form of gestational trophoblastic neoplasm which is distinct based on its development from intermediate trophoblast cells and nodular growth pattern. The aim of this study is to describe a case series from a single institution with a review of the literature to better understand the clinical characteristics and outcomes for patients with ETT.

Methods. A retrospective review was performed using the IRB approved New England Trophoblastic Disease Center (NETDC) database from 1998 to 2014. Eight patients were identified of which seven had complete records. Follow-up data was obtained from the longitudinal medical records.

Results. Four (57.1%) patients presented with vaginal bleeding and two (28.6%) patients were asymptomatic at presentation. Three (42.9%) patients had extrauterine disease. All three patients with extrauterine disease who received chemotherapy had stable or progressive disease at follow-up. Only two (29%) patients who presented with non-metastatic disease and underwent hysterectomy were alive with no evidence of disease. The mean interval following antecedent pregnancy was 104 months. All patients with an interval >4 years demonstrated stable or progressive disease despite intensive chemotherapy. Two patients with non-metastatic disease who declined hysterectomy developed stable or progressive disease despite chemotherapy.

Conclusions. This series highlights several features of ETT including the potential for asymptomatic presentation of extrauterine disease. The series also demonstrates chemoresistance, even with multi-agent therapy and a poor prognosis with extrauterine disease and an interval greater than 4 years following the antecedent pregnancy suggesting that surgery remains critical in disease control.

1. Introduction

Epithelioid trophoblastic tumor (ETT) is an extremely rare form of gestational trophoblastic neoplasia (GTN) representing less than 2% of all gestational trophoblastic diseases [1]. The first report, a series of 14 cases by Shih and Kurman in 1998, described this unique type of tumor comprised of chorionic type intermediate trophoblastic cells distinct from placental site trophoblastic tumor (PSTT) and choriocarcinoma with features that more closely resembled carcinoma [2,3]. Clinically, these tumors have been shown to present predominantly in reproductive age women with 67% of antecedent gestations being a full term pregnancy [2,4,5]. This population is also unique in that it has been shown to have a delayed interval to presentation, with reports ranging from 1–18 years following the antecedent pregnancy [2,5,6]. Case reports have demonstrated that patients with ETT typically present with vaginal bleeding and will often have an elevated beta human chorionic gonadotropin (hCG) yet are frequently misdiagnosed pre-operatively, largely because of their rarity and diverse presentation [2,4,7]. Pathologic findings have been described as a nodular growth of nested and corded

* Corresponding author.

http://dx.doi.org/10.1016/j.ygyno.2015.03.006
0090-8258/

monomorphic, epithelioid cells often with areas of necrosis [4]. These tumors may be confused with squamous cell carcinomas because of their common location in the lower uterine segment and cervix and positive staining for cytokeratin and p63 [2,4]. ETT differs from PSTT in its nested, nodular growth unlike the sheet-like and highly infiltrative growth pattern seen in PSTT [4]. ETT shares some clinical and pathologic characteristics with PSTT including slow growth rates, development from intermediate trophoblastic tissue, relatively low hCG levels, and poor response to chemotherapy making the management of this rare tumor even more challenging [2,8].

Similar to other gestational trophoblastic diseases, the mortality associated with ETT remains low, though the rate of metastasis has been reportedly higher ranging from 25–88.9% [2,6,9]. The WHO scoring system has limited utility in PSTT and ETT unlike other forms of GTD [8,23]. Factors associated with poor prognosis in PSTT include metastatic disease and interval greater than 4 years from the antecedent pregnancy [8,10]. There have been limited prognostic indicators identified for ETT, though these may be similar to those described previously for PSTT. There have been several case reports and small case series since the initial publication by Shih and Kurman in 1998 though the data remains limited. Scott et al. published a case report with a review of the literature in 2012 and described a total of 94 published cases [5]. Using a MEDLINE search, since 2012 there have been eleven additional publications for a total of 14 new cases, accounting for 108 reported cases in the literature [4,6,20–22].

ETT is a rare tumor and despite several small series, the clinical course and presentation remain complex and varied, making the diagnosis and management challenging. Furthermore, other tumors of epithelial origin may mimic ETT and without the aid of immunohistochemical or genetic analysis, may be difficult to distinguish [2]. The aim of this study is to review a series of cases treated at a single institution, the New England Trophoblastic Disease Center (NETDC). This study highlights the clinical presentation, treatment, and outcomes of patients diagnosed and treated with ETT at the NETDC to provide further information regarding this rare malignancy while describing a unique case of an asymptomatic presentation of ETT with extrauterine disease.

2. Methods

After obtaining institutional review board (IRB) approval for this project, we conducted a retrospective chart review of all patients in the NETDC database who were diagnosed and treated with ETT from 1998 to 2014. We identified eight patients seen in consultation or treated at NETDC. The pathologic diagnosis of ETT was confirmed by three subspecialty gynecologic pathologists with the aid of immunohistochemical and genetic markers when available. One patient had a composite tumor of both ETT and choriocarcinoma. One patient was excluded due to insufficient clinical follow-up data available for analysis. The remainder of the clinical information was extracted from the electronic longitudinal medical record.

Patients were followed at the NETDC or with their primary provider following their definitive treatment with weekly hCG values until undetectable for three weeks, then monthly for one year. If the patient lived at a substantial distance from Boston such that the above follow-up could not be achieved, this was performed at their local institution and information on clinical status and follow-up was requested on a monthly basis. The hCG assay utilized at our institution demonstrates an undetectable result with values less than 2 mIU/mL. For patients at a distance, clinicians were encouraged to use the most sensitive assay available.

3. Results

Seven patients were included in the series with diagnosis between 2010 and 2014. No patients were identified in the database with pathologically confirmed ETT prior to 2010. The mean age at presentation was 39.7 years (range 31 to 51 years) including two postmenopausal patients. The symptoms at presentation varied, with the majority (57.1%) of patients experiencing vaginal bleeding. However, two patients were entirely asymptomatic at the time of diagnosis. In one patient (Case 5), ETT was diagnosed in an umbilical hernia repair specimen and in one patient (Case 1), ETT was diagnosed in a morcellated laparoscopic myomectomy specimen. One patient (Case 7) presented with pain at the site of a prior cesarean section scar and was found to have a 9 cm mass in the left rectus abdominis muscle abutting the deep fascia which was diagnosed as ETT on pathologic examination following wide local excision. The majority of cases (57.1%) were confined to the uterus, presenting in the fundus or lower uterine segment similar to the locations originally described by Shih and Kurman, though no patient presented with an endocervical tumor as has been described in the literature [2,6]. No patient had radiographic disease above the diaphragm at diagnosis. Three patients (42.9%) had extrauterine disease at the time of diagnosis.

In regards to obstetric history, six (85.7%) patients had a documented antecedent pregnancy prior to diagnosis; one patient (Case 1) was thought to be nulliparous but was found to have ETT at the time of laparoscopic myomectomy, likely with an undocumented spontaneous abortion. Two patients had an antecedent molar pregnancy (Cases 3 and 4) and in Case 4 the only prior pregnancy being a partial mole. The mean time interval for all cases from antecedent pregnancy to diagnosis of ETT was 104 months (range 12 to 264 months). Four patients (57.1%) presented following a full term delivery, two of which had an antecedent vaginal delivery and two underwent a cesarean section. Two patients had a bilateral tubal ligation prior to their diagnosis of ETT.

Four patients (57.1%) had serum human chorionic gonadotropin (hCG) levels less than 10 at the time of diagnosis and two of those patients had undetectable hCG levels. The median hCG value was 9 (range 1 to 538,330 mIU/mL). The two patients who presented with hCG values > 100,000 both had an antecedent molar pregnancy. Patients with an initially elevated hCG had their values followed similar to standard monitoring for gestational trophoblastic neoplasia (GTN) and the hCG levels were a useful marker of clinical response.

All patients underwent surgical intervention, four (57.1%) of which were treated with hysterectomy. Two additional patients (Case 1 and Case 4) were recommended hysterectomy but declined given their desire for ongoing fertility. One subsequently developed a cervical recurrence with stable uterine disease on recent biopsy and the other was lost to follow-up but had progressive disease at that time. Patients with extrauterine disease underwent multiple surgical procedures with a mean number of three surgical procedures for all cases. Six patients (85.7%) received chemotherapy, which included chemotherapy initially used to treat presumed GTN prior to the diagnosis of ETT. Four patients (57.1%) underwent a multiple agent regimen consisting of etoposide, methotrexate, actinomycin-D, cisplatinum (EMA-EP) for the treatment of ETT [11]. The number of cycles received varied ranging from two to nine cycles with only one patient stopping chemotherapy for associated toxicity. Two patients (28.6%) had no evidence of disease at the time of follow-up. Both of these patients underwent surgical management with hysterectomy and had disease confined to the uterus. Two patients (28.6%) had stable disease and three patients (42.9%) had progressive disease with metastasis to the lung, vagina, and pubic symphysis at the time of follow-up. While the review by Palmer et al. demonstrated 13% of patients dead of disease with follow-up ranging from 1–39 months; no patient in this series was dead of disease during a similar follow-up period of 3–40 months [6]. The mean follow-up in this series was 24.0 months. Table 1 outlines the individual clinical outcomes for all cases. Supplemental Table 1 addresses the pathologic variables for all cases when available including mitotic count, lymphovascular invasion, and depth of invasion. Case 5 will be highlighted in more detail given the unique presentation and pathology. Furthermore, to our knowledge, a presentation of asymptomatic, extrauterine disease with heavily calcified tumor has never previously been reported in the literature.