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Case report

Primary mediastinal choriocarcinoma in a female patient: Case report and review of the literature

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1. Background

Primary non-gestational mediastinal choriocarcinoma is a rare germ cell malignancy that is diagnosed in the absence of a primary tumor in the gonads or metastatic disease in the retroperitoneal lymph nodes. It represents 1–4% of all mediastinal tumors and < 5% of all germ cell malignancies (Tanaka et al., 2017). Non-gestational choriocarcinoma can be differentiated from gestational choriocarcinoma as the latter is a type of gestational trophoblastic neoplasia associated with a prior molar or normal pregnancy. It is important to make a distinction between the two forms of choriocarcinoma as non-gestational is very rare and carries a poorer prognosis. Demographically, primary non-gestational mediastinal choriocarcinoma is noted to be more prevalent in men than in women and is a clinically aggressive disease despite treatment. Symptoms at the time of presentation frequently include dyspnea, chest pain, cough, or other common features of metastatic disease. Elevated human chorionic gonadotropin (hCG) levels typically aid in the diagnosis. We present a case of primary mediastinal choriocarcinoma in a female patient with a brief review of the literature.

2. Case presentation

53 year old Gravida 3 Para 3 woman presented to our clinic as a referral for further evaluation and treatment of metastatic choriocarcinoma. Prior pregnancy records were unavailable though she had three prior term deliveries, one of which was via cesarean section. At the time of presentation, documentation noted three living adult children. She had initially presented with week-long complaints of diplopia and subsequent difficulty balancing in addition to cough, fatigue, and a one month history of dyspnea on exertion.

She then presented to the Emergency Department ten days later after multiple falls at home with injury to her head and chest. A computed tomography (CT) of her head was performed and demonstrated three hyper-dense intra-axial masses concerning for metastatic disease. Subsequent head magnetic resonance imaging (MRI) identified four metastatic intracranial lesions. Further imaging was obtained including CT of the chest, abdomen and pelvis which revealed a mediastinal mass consistent with a 7 × 9 cm coalescent malignant adenopathy. The CT also demonstrated a 1.4 cm rounded left axillary lymph node, concern for splenic metastasis, and suspicious lesions in the iliac bones.

Mediastinoscopy and biopsy of the large mass identified high-grade carcinoma, morphologically and immunophenotypically consistent with choriocarcinoma. Tumor markers including hCG, alpha fetal protein (AFP), and lactate dehydrogenase (LDH) were negative.

Immunohistochemistry was performed including CK pool, CK5/6, CK-7, CK-20, Hepatocyte, p63, melan A, S100, CD5, CD117, TTF-1, WT-1, PLAP, GATA-3, AFP, OCT4, CD30 and hCG. The tumor cells stained strongly positive with CK pool, CK-7, PLAP and GATA-3. There was focal positivity with CK5/6 and hCG. The tumor cells were negative for CK20, Hepatocyte, p63, melan A, S100, CD5, CD117, TTF-1, WT-1, CD30, AFP, and OCT4. The immunophenotypic pattern with positive staining for CK pool, PLAP, GATA-3 and focal positivity with hCG supported the diagnosis of choriocarcinoma.

Tissue pathology was consistent with the immunohistochemistry findings of choriocarcinoma. Histologic analysis was suggestive of pleomorphic malignant neoplasm with cellular findings of abundant pink cytoplasm, indistinct cell borders, scattered multinucleated giant cells, focal somewhat lacy cytoplasm and abundant necrosis (Fig. 1).

Array comparative genomic hybridization (aCGH) was obtained to evaluate for tumor genome imbalances. Gain of the chromosomal region from 2p16 to 2p terminal, and losses of or from 6p, 6q12q22,

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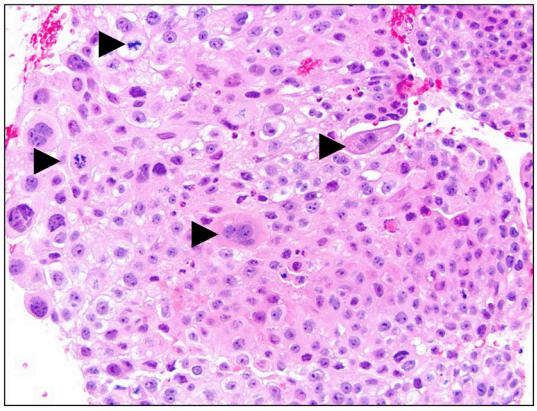

Fig. 1. Histologic features of poorly differentiated mediastinal mass. Hematoxylin & eosin stained sections of the tumor showed a biphasic pattern of malignant epithelioid cells and intermixed multinucleated giant cells (arrowheads). Mitotic features were easily found (arrows). Tumor cells were positive for placental alkaline phosphatase (PLAP) with patchy human chorionic gonadotropin (hCG)—data not shown. Photo taken with Leica microscope using 40× objective.

6q23, 9p, 10q21q25, 13q and 22q were seen.

(Rev ish enh(2p16pter),dim(6p,6q12q22,6q23pter,9p,10q21q25, 13q,22q).

Ultimately, the patient received palliative whole brain radiotherapy (400 cGy × 5 to 20 Gy) and VIP chemotherapy (Etoposide, Cisplatin, and Ifosfamide). After two cycles of chemotherapy without improvement in symptoms she declined any further treatment and deceased six months after initial diagnosis.

3. Discussion

Non-gestational choriocarcinoma of the mediastinum is a rare malignancy, especially in women. Few cases of this disease have been described in female patients (Table 1); thus, this case report aims to increase the knowledge available in the literature.

The mechanism by which primary mediastinal non-gestational choriocarcinoma develops is poorly understood. Postulated theories include: (1) metastases from a primary gonadal choriocarcinoma that regressed spontaneously; (2) origin from a trophoblastic embolus related to a gestational event after a long period of latency; or (3) origin from retained primordial germ cells that migrated abnormally during embryogenesis (Fine et al., 1962; Br Med, 1969; Cohen and Needle, 1975; Forest et al., 1977; Lam et al., 2011; Zhang et al., 2014a; 2014b; Kuno et al., 2016; Zhang et al., 2016; Francischetti et al., 2017).

Currently, little data exist regarding the most efficacious treatment for primary non-gestational mediastinal choriocarcinoma. Surgery, radiation, and chemotherapy remain the mainstays of treatment at this time though prognosis remains poor despite varied treatment options and modalities. As might be expected, outcomes tend to improve following a combination of surgery and chemotherapy (Zhang et al., 2014a). Table 1 highlights some of the different chemotherapy regimens that have been used in past cases, many of which are based on treatment protocols for advanced germ cell tumors.

Serologic tumor markers are important in the diagnosis of mediastinal germ cell tumors with elevated hCG levels present in 30% of mediastinal non-seminomatous carcinomas (Rosado-de-Christenson et al., 1992). Interestingly, hCG levels were negative in our patient.

Cytogenetic analysis of germ cell tumors (GCTs) has identified an isochromosome of the short arm of chromosome 12, i(12p), as a specific cytogenetic abnormality identified in > 80% of GCTs (Ilson et al., 1991). It is present in all histologies, primary and metastatic lesions, testicular and extragonadal presentations, and in ovarian and sex cord stromal tumors. Identification of i(12p) in poorly differentiated midline carcinomas of uncertain histogenesis can thus assist in the diagnosis of GCT (Ilson et al., 1991). We found no gain of 12p genetic material in the present case, where also genomic losses were predominant. The latter finding has not been previously reported in this type of germ cell tumor. Loss of chromosomes 13 and 22 are common in classic cytogenetic analysis of teratomas, seminomas, and germinomas. In addition, loss of chromosomes 13 and 22 together with structural rearrangements of chromosome 6 has been reported in more than thirty such tumors (Mertens, 2018). The only genetic gain in our case involved the short arm of chromosome 2 (2p). The largest study of aCGH in choriocarcinomas included twelve cases and identified genomic imbalances in 9 of the twelve cases with a recurrent deletion in 8p (5 cases) and amplification of 7q material (4 cases) (Ahmed et al., 2000).

In summary, our case of non-gestational mediastinal choriocarcinoma was notable for its absence of hCG production and typical gain of 12p material, requiring histologic diagnosis. The genomic markers found in our case add to the existing body of literature regarding markers associated with this rare form of malignancy. Due to its rarity, there currently exists no consensus regarding treatment protocols. This malignancy unfortunately carries a poor prognosis. Thus, case reports such as ours contribute to the scant literature to assist in the diagnosis of these aggressive tumors.

Table 1
Primary non-gestational mediastinal choriocarcinoma: a summary of the literature.

Authors (reference)	Cases reviewed	Sex ratio	Age range	Chemotherapy regimens	Range of survival
Fine et al. (1962)	19 possible, 9 proven	Male	19–60	NA	NA
British Medical Journal, (Br Med (1969))	20	19 Male 1 Female	20–30	NA	4 weeks – 6 months after symptoms
Cohen and Needle (1975)	1	9 Male 2 Female	50% in 30s	Methotrexate, chlorambucil, actinomycin D	< 5 years
Forest et al. (1977)	2	2 Male	26–45	Actinomycin D alone; actinomycin D, cyclophosphamide, vincristine	10 days to 2 months
Lam et al. (2011)	1	Male	25	Dexamethasone, cytarabine, cisplatin	2 weeks
Zhang et al. (2014a)	6	Male	NA	Variable; case report with etoposide, cisplatin	6 weeks to 1 year
Zhang et al. (2014b)	44	40 Male 4 Female	NA	Unavailable; patient in report received EMA-CO	NA
Kuno et al. (2016)	1	Female	58	Etoposide, MTX, dactinomycin, cyclophosphamide, vincristine	41 days
Zhang et al. (2016)	1	Male	25	Chemoradiation with etoposide, cisplatin, bleomycin	Survival > 16 months at time of publication
Francischetti et al. (2017)	1	Male	41	VIP (etoposide phosphate, ifosfamide, cisplatin)	NA

Conflict of interest statement

The authors whose names are listed certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Author contribution

Samantha Batman is the primary author who wrote the majority of the manuscript and performed the literature review. Terry Morgan is a pathologist who performed the immunohistochemical stains. Marta Brunetti, Rønnaug A.U. Strandabø, and Francesca Micci are experts in cytogenetics who consulted on the array comparative genomic hybridization. Melissa Moffitt is a gynecologic oncologist who was the patient's primary oncologist and determined her treatment plan. Tanja Pejovic is a gynecologic oncologist who oversaw this collaboration and also contributed to the writing of the manuscript.

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