

Cancer of Unknown Primary During Pregnancy: An Exceptionally Rare Coexistence

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Abstract. *Background:* Cancer in pregnancy is a rare disease with breast cancer, cervical cancer, melanoma and Hodgkin's disease to be the most commonly diagnosed malignancies during gestation. Cancer of unknown primary (CUP) is a well-recognized clinical disorder where the primary site can not be identified after a standard diagnostic approach. CUP in pregnancy has rarely been described. *Materials and Methods:* We searched MEDLINE and contacted cancer Centers in Europe, United States and Australia where patients with CUP or pregnant patients with cancer were diagnosed and treated. *Results:* Since 1976 we identified 18 pregnant women with CUP in a median gestational age of 34 weeks. Most of these patients were diagnosed with poorly-differentiated histology, had poor response to systemic treatment and a median maternal survival of 8 months. Seventy-two percent of mothers have died, while 80% of the newborns were alive and healthy. Almost one fourth of placentas examined showed metastatic disease. *Conclusion:* CUP during pregnancy is a very rare coexistence, usually has an aggressive disease with poor response to chemotherapy and a dismal prognosis. Both obstetricians and oncologists should be aware of this rare condition.

Cancer of unknown primary (CUP) is defined as a malignant tumor that presents with early disseminated disease without detectable primary site. It accounts for 3-5% of all cancers and it is usually characterized by an aggressive behavior with an unpredictable natural history. CUP is divided into two different clinicopathological entities, the unfavorable and the favorable groups. Unfavorable cases represent 80% of all CUP patients

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and are associated with a relative chemoresistance and a dismal prognosis. Histologically, 60% are diagnosed as adenocarcinomas of well or moderate differentiation, 30% as undifferentiated or poorly-differentiated adnocarcinomas and the remaining 10% as squamous cell carcinomas or undifferentiated neoplasms (1, 2).

Pregnancy can rarely be complicated by the presence of various malignancies. Gestational cancer requires specific "optimal gold standards" because it involves two persons, the mother and the fetus. These patients should be treated within a multidisciplinary team in experienced centers. The incidence of this coexistence is 1 out of 1,000 pregnancies with breast cancer, cervical cancer, melanoma and hematological tumors representing the most common tumors found during pregnancy (3, 4). CUP is the rarest form of cancers diagnosed during gestation with very few cases reported during the last 40 years.

The main goal of this article is to review all published studies existing in the English literature and in addition to collect unpublished cases from major cancer centers from both Europe and USA. We present the clinical and histopathological characteristics of each CUP case and emphasize on the therapeutic management, as well as the maternal and fetal outcome.

Materials and Methods

We searched MEDLINE on the following search terms: "Cancer of Unknown Primary and Pregnancy", "Cancer of Unknown Primary and Gestation", "Metastases from Unknown Primaries and Pregnancy" and "Krukenberg Tumors and Pregnancy".

In addition, we contacted cancer centers in Europe, United States and Australia where patients with CUP or pregnant patients with cancer were diagnosed and treated. We elicited 11 relevant publications from the English literature and we have been able to collect 7 unpublished cases from USA, UK and Italy treated at Nashville Sarah Cannon Cancer Center, Saint George's Hospital, London and Milan European Institute of Oncology, respectively.

Table I. Patients' characteristics.

| | |
|--|----------------------------------|
| Number of cases | 18 (11 published, 7 unpublished) |
| Maternal age (median) | 35.5 (25-41) years |
| Gestational age (median) | 34 (15-39) weeks |
| Country of origin | |
| US | 9 |
| UK | 3 |
| Italy | 2 |
| Spain | 1 |
| Israel | 1 |
| Japan | 1 |
| India | 1 |
| Histopathology | |
| Moderately, Poorly, differentiated carcinoma | 13/18 (72%) |
| Undifferentiated carcinoma | 1/18 (5.5%) |
| Other | 4/18 (22.5%) |
| Metastatic sites | |
| Nodes | 12/18 (67%) |
| Liver | 8/18 (44%) |
| Bones | 7/18 (39%) |
| Lung/pleura | 5/18 (28%) |
| Pelvis/ovaries | 5/18 (28%) |
| Peritoneal/omental | 3/18 (17%) |
| Retroperitoneum | 3/18 (17%) |
| Cutaneous | 3/18 (17%) |
| Other rare sites | 10/18 |

Results

Patients' characteristics. Overall, 18 patients, 11 cases from the English literature and 7 from various European and American Cancer Centers were included. The median maternal age was 35.5 years (range, 25-41) and median gestational age at diagnosis was 34 weeks (range, 15-29). CUP was diagnosed in 2 patients during the postpartum period.

Histopathological characteristics. In 12/18 (66.6%) patients, the histology confirmed poorly-differentiated carcinoma, adenocarcinoma or epidermoid carcinoma. Of the remaining 6 cases one patient had moderately to poorly-differentiated carcinoma (5.5%), one had undifferentiated carcinoma (5.5%), one infiltrating adenocarcinoma with extensive desmoplasia (5.5%), one undetermined metastatic carcinoma in the bone marrow (5.5%), one had metastatic mucinous adenocarcinoma (5.5%) and one was diagnosed with serous peritoneal neoplasm of low malignant potential and diffuse microinvasion (5.5%).

Metastatic sites. The most common metastatic lesions were found in lymph nodes (67%), liver (44%), bone (39%), lungs (28%) and pelvis (28%), followed by peritoneum (17%), retroperitoneum (17%) and subcutaneous tissue (17%). Rare

metastases were also detected in adrenals, spleen, bone marrow, urinary bladder, intestines, diaphragm, heart, muscles, breast and CNS meningeal structures (Table I).

Treatment

Surgery. Six patients (33%) underwent an excisional biopsy, 5 (28%) had one or more exploratory laparotomies with or without debulking surgery, one patient had an open lung biopsy and one laparoscopic biopsy. Five patients never had any surgical procedure and diagnoses in these cases were made by fine needle aspiration.

Chemotherapy. First-line systemic chemotherapy for advanced disease was administered in 14 patients (77.5%); in three of them in the adjuvant setting. Second or third-line chemotherapy was given in 4 patients following failure of first-line treatment. Targeted-treatment with trastuzumab and vemurafenib was given to 2 patients. Most patients (72%) were treated during the postpartum period a few weeks after delivery. Four patients had no chemotherapy at all. Chemotherapy included platinum combinations with taxanes, doxorubicin, gemcitabine or cyclophosphamide (Table II).

Maternal and fetal outcome. Regarding delivery of babies, 44% of women underwent a cesarean section, whereas 39% had a normal vaginal delivery.

Table II. *Therapeutic management of CUP.*

| | | |
|---|-------|---------|
| Surgery | | |
| Excisional biopsy | 6/18 | (33%) |
| Exploratory laparotomy (\pm debulking) | 5/18 | (28%) |
| Open lung biopsy | 1/18 | (5.5%) |
| Laparoscopy / biopsy | 1/18 | (5.5%) |
| No surgery | 5/18 | (28%) |
| Chemotherapy | | |
| 1st-line* | 14/18 | (77.5%) |
| 2nd-line | 4/18 | (22.5%) |
| Adjuvant setting | 3/18 | (17%) |
| Targeting treatment ** | 3/18 | (17%) |
| During postpartum | 13/18 | (72%) |
| During pregnancy | 1/18 | (5.5%) |
| No chemotherapy | 4/18 | (22.5%) |

*Mostly platinum-based (77.5%); **trastuzumab, vemurafenib. CUP, cancer of unknown primary.

Table III. *Maternal and fetal outcome.*

| | | |
|--------------------------------|------------------------|---------|
| Delivery | | |
| Caesarian section | 8/18 | (44%) |
| Vaginally | 7/18 | (39%) |
| Spontaneous labor | 1/18 | (5.5%) |
| Surgical termination | 1/18 | (5.5%) |
| Intrauterine death | 1/18 | (5.5%) |
| Mother's outcome | | |
| Dead | 13/18 | (72%) |
| Alive | 5/18 | (28%) |
| Median survival from diagnosis | 8 months | |
| | (12 hours – 37 months) | |
| Newborns' outcome | | |
| Premature | 4/16 | (25%) |
| Alive and well | 12/15 | (80%) |
| Dead * | 3/15 | (20%) |
| Unknown | 3/18 | |
| Placental metastases | 4/18 | (22.5%) |

*Intrauterine death, surgical termination, spontaneous labor.

Thirteen (72%) patients have died with a median survival of 8 months from diagnosis. Five patients were still alive, two with no evidence of disease between 24-32 months, following surgery or after chemotherapy. The other three women were still alive with survival ranging from 8 to 37 months and are in partial remission or have stable disease.

The outcome of the newborn babies was as follows: 80% of them remain alive and healthy, 25% were premature and three died. The causes of death were one intrauterine death, one surgical termination at 17 weeks of gestation and one from placental abruption and disseminated intravascular coagulation due to placental metastases. Data on three newborns were missing. In four patients metastatic lesions were found in the placentas. No metastases were detected in any of the newborns.

Discussion

Cancer in pregnant mothers is a dramatic event and represents an uncommon biological paradox. In this very rare coexistence, both obstetricians and oncologists should offer at the same time optimal maternal treatment and possibly fetal preservation, trying to protect both mother and fetus from the harmful effects of diagnostic procedures or therapeutic applications (3, 4).

The commonest malignant tumors diagnosed during gestation are those cancers with a peak incidence during the woman's reproductive period, such as mammary and cervical carcinomas, melanomas, lymphomas or leukemias. Unfortunately, during the last decades, modern society is experiencing a change in attitude to fertility with many women choosing to delay pregnancy into the later reproductive years. In the light of that change, we are probably going to face more cancers in pregnant women in the coming years. The median maternal age of our patients was already 35.5 years.

CUP is a syndrome consisting of various hidden primary tumors with an incidence of 3-5% of all cancers and a median age at diagnosis around 65 years. Therefore, CUP during pregnancy remains an extremely rare diagnosis. CUP is separated into favorable and unfavorable groups. The favorable subsets of isolated adenocarcinoma of the axillary nodes, as well as of primary peritoneal serous papillary adenocarcinomas, are equivalent to primary breast and ovarian cancers and can be diagnosed at relatively younger ages (5, 6). Three of our patients who enjoyed more than two years survival had histopathological and clinical findings compatible with the above favorable CUP subsets (7, 9). Information of BRCA mutations in these particular groups of CUP patients would be of a great interest.

The majority of the cases in the present article were diagnosed with poorly-differentiated or undifferentiated carcinomas and with mainly visceral, bone and nodal metastases. The median survival was only 8 months, indicative of an aggressive type of cancer (10-17).

During pregnancy, diagnostic imaging modalities with computed tomography or positron emission tomography should be avoided due to radiation effect on the fetus. However, magnetic resonance can be used in certain cases with caution (18, 19). A molecular diagnostic approach for the detection of the primary site has been recently developed. The accuracy rates of gene expression profiling in the classification of tumor types are as high as 93% (20, 21). Whether the biological definition of tissue of origin in CUP poorly-differentiated cases during pregnancy could be an additional diagnostic tool, remains to be answered.

CUP patients with favorable subsets are initially treated with locoregional treatment i.e. surgery or radiotherapy

followed in certain cases by chemotherapy or hormone-therapy. In other favorable entities, such as primary peritoneal carcinoma or neuroendocrine tumors, the treatment of choice is mainly systemic therapy. Responses and survival can be promising with some long-term survivors (1, 2). However, cases within the unfavorable group are usually treated with empirical chemotherapy with poor results (22, 23). Most of the patients in this review were treated with chemotherapy during the postpartum period and experienced a poor outcome.

Chemotherapy can be recommended, if needed, during the second and third trimester of pregnancy, whereas is not safe in the first trimester due to the potential risks of induced malformations, mutagenesis or teratogenesis. Among the various hemotherapeutic drugs, alkylating agents, anthracyclines, platinum-derivates and taxanes are considered safe for treating pregnant women with cancer. Endocrine treatment including tamoxifen or aromatase inhibitors, as well as targeted treatment with trastuzumab or tyrosine kinase inhibitors, should be avoided due to gestational complications or due to limited experience (24, 25). Almost 80% of our patients have been treated with platinum – based chemotherapy as a first- or second-line treatment.

Metastatic transmission to placenta or fetus is a very rare complication of cancer during pregnancy. There are total of 100 cases of placental involvement reported, with melanoma being the most common tumor (30%), followed by lung cancer (21%), hematological malignancies (17%) and breast cancer (14%), while fetal metastases have been recorded in only 17 cases (26, 27). In our study, 4 patients were diagnosed with placental metastases, an incidence of 22.5%, which characterize CUP as one of the commonest cancer during gestation with high predilection for placental invasion. Taking into consideration that placentas in pregnant women with cancer should always be submitted to histological examination, the lack of such information in some of our cases might underestimate the real incidence of placental involvement in pregnant patients with CUP. None of the newborns in this study were found to have metastatic lesions on clinical examination. In line with this, fetal outcome is usually good with most of the newborns still alive and healthy. Eighty percent of the newborns in this study were alive and well.

In conclusion, this is the first review of the available literature to collectively report on the coexistence of CUP during pregnancy. Since 1976, we have been able to collect only 18 cases indicating the exceptional rarity of this coexistence. It should also be emphasized that CUP in pregnant mothers behaves as an aggressive disease with poor histopathological characteristics leading to a dismal outcome and survival.

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