Burkitt's lymphoma related to Epstein–Barr virus infection during pregnancy

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Abstract

Setting Burkitt's lymphoma is a rare form of cancer and is an extremely rare diagnosis during pregnancy. This form of lymphoma is a very fast growing B cell neoplasm and chemotherapy is the treatment of choice for the disease in all its stages.

Case report The authors describe the case of a Caucasian 40-year-old nulliparous woman, with previous known Epstein–Barr virus infection, that presents at 28 weeks gestation with supraclavicular adenopathy and multiple bilateral breast nodules, in which biopsy showed non-Hodgkin lymphoma, Burkitt's type.

Discussion There are few described cases of Burkitt's lymphoma during pregnancy and in general the outcomes have been poor. In most of the cases, the patients were not treated by current standards or instead had a late diagnosis. This neoplasia is the most rapidly progressive human tumor, and any delay in initiating therapy can adversely affect patient's prognosis. The authors discuss treatment options in pregnancy and its perinatal implications.

Keywords Burkitt's lymphoma · Pregnancy · Chemotherapy

Introduction

Burkitt lymphoma (BL) is a rare non-Hodgkin lymphoma that results from B lymphocytes monoclonal proliferation, making less than 1% of non-Hodgkin lymphomas in adults. This high-grade B cell neoplasm is one of the most aggressive malignancies known and, although it is typically a childhood disease, it can be observed in adults. However, BL is rare during pregnancy. The infection with Epstein–Barr virus (EBV) has strong association with the African form, while it is associated only with about 15–30% of sporadic cases [6, 8, 10]. The purpose of this report is to present a case of BL related to EBV infection during pregnancy and to discuss obstetric and perinatal implications of adequate treatment.

Case report

A 40-year-old Caucasian woman, G2 P0, with a pregnancy of 27 weeks gestation was referred to our maternal–fetal department for evaluation of supraclavicular lymphadenopathy. The patient had no history of fever or weight loss but referred night sweats and recent breast enlargement. She had a history of EBV infection with cervical lymphadenopathies 2 years before, and pregnancy had been uneventful until that time. On examination, there was a left supraclavicular lymphadenopathy with 2×1.5 cm and multiple tender nodules with less than 2 cm on both breasts. The chest and abdominal examination had no other alterations and pelvic examination

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revealed the uterus to be the size of 27 weeks gestation with fetal heart tone audible with Doppler instruments. Ultrasound demonstrated an appropriately grown fetus with normal biophysical profile. She was immediately referred for hematology consultation and supraclavicular adenopathy aspirative cytology was done with the diagnosis of Non-Hodgkin B cell lymphoma, Burkitt type, with the translocation (8;14) on cytogenetic analysis. By that time results of human immunodeficiency virus (HIV) antibody tests were negative and serology for EBV confirmed persistent infection (with qualitative polymerase chain reaction positive for EBV-DNA). Tumor cells in situ hybridization for EBER (Epstein–Barr encoded RNA) was positive. Biopsy of breast nodules also revealed breast tumor infiltration and bone marrow aspiration and biopsy was positive with 30% Burkitt cells infiltration. Lumbar puncture excluded central nervous system (CNS) involvement. Chest MRI showed multiple left latero-aortic lymphadenopathies. The abdominal and renal ultrasound scans were unremarkable. Laboratory data revealed hemoglobin 11.1 g/dL with 32.2% hematocrit, normal white blood cell count and platelet count of 117,000/ μ L. The serum chemistry profile revealed uric acid 5.0 mg/dL, lactic dehydrogenase 937 UI/L and normal aminotransferases.

The patient was counseled regarding the importance of initiating chemotherapy, despite the potential risks to her fetus. After consultation between pediatrics and maternal–fetal medicine departments, the patient was offered and accepted starting aggressive chemotherapy immediately and, once fetal lung maturity was accomplished, having a cesarean section to continue adequate treatment outside pregnancy. At 28 weeks gestation she began induction chemotherapy, as stated by the French R-LMB protocol: rituximab, cyclophosphamide, vincristine and methylprednisolone. The patient also received CNS prophylaxis consisting of intrathecal prednisolone alone, instead of the usual prednisolone, methotrexate and arabinosylcytosine, because of concerns for the potential toxic effect of the latter two on the fetus. Betametasone was administered for fetal lung maturation.

After 5 days of induction chemotherapy, with stable laboratory data, she was submitted to cesarean section. She delivered a healthy 1,263 g girl with Apgar Scores of 9 and 9 (respectively, at 1' and 5') with no signs of myelosuppression. The newborn was admitted to neonatal intensive care unit and, despite initial respiratory distress syndrome and omphalitis, had good evolution, and was discharged in adequate condition at 46 days of age. Placenta had no signs of BL infiltration on pathological examination. After delivery the patient continued on the treatment protocol and was disease-free one year after end of therapy. The polymerase

chain reaction for EBV-DNA became negative in the end of the treatment.

Discussion

BL is a high-grade B cell neoplasm that was initially described by Dennis Burkitt as a jaw sarcoma occurring in East African children [4]. Today, three major forms of BL are recognized: the endemic (African) form, the sporadic (non-endemic) form and the immunodeficiency-associated form. Endemic cases occur in African children and sporadic ones are seen worldwide, being also more frequent in children (it accounts for 40% of lymphomas in children) [6]. On the other hand, immunodeficiency-associated lymphoma occurs in patients with HIV infection and allograft recipients [1, 6]. EBV infection is found in nearly all cases of endemic lymphoma however, in sporadic forms, EBV is found in only 15–30% of the cases [10].

BL can be morphologically diagnosed with high degree of accuracy since it has typical histologic findings: burkitt cells are homogeneous in size and shape, with round to oval nuclei and slightly coarse chromatin, with multiple nucleoli, and with intensely basophilic vacuolated cytoplasm; frequent mitotic figures are observed; and a “starry sky” appearance is imparted by scattered macrophages with phagocyte cell debris. A defining feature of BL is the presence of translocation between the *c-myc* gene and the *IgH* gene—*t*(8;14) found in 80% of the cases—or between *c-myc* gene and the gene of either kappa or lambda light chain (*IgL*) in the remaining 20% [*t*(2;8) or *t*(8;22), respectively] [1, 3, 4, 6, 9]. These translocations take place within regions that undergo chromosome breakage during maturation of germinal center B cells, fact that favors the argument that translocations are mistakes that occur during normal B cell development, leading to *c-myc* expression deregulation and driving cells through the cell cycle with activated antiapoptotic pathways. So, in all BL variants the key factor in the oncogenesis is the constitutive activation of the *c-myc* oncogene through its translocation into one of the immunoglobulin loci [10, 13].

The role of EBV infection in the pathogenesis of BL remains hypothetical. EBV-positive cases usually exhibit a highly restrictive pattern of expression of latent encoded proteins, (called type I latency program), expressing only EBNA1 (Epstein–Barr Nuclear Antigen-1, considered the viral genome maintenance protein) and EBERs (Epstein–Barr Encoded RNAs, nonpolyadenylated RNAs used for clinical detection because of their abundant expression). One hypothesis is that EBV works as a potentiator of tumor formation acting early in the lymphomagenic process by increasing the frequency of genomic instability within the infected B cell population and thus increasing the probability

of a new *c-myc* translocation. Alternatively persistent EBV infection could provide a biological advantage for the tumor cell somehow increasing the lymphomagenic potential of a *c-myc* translocation-positive cell. In fact, it is known that EBNA1 plays a crucial role in the maintenance and replication of the viral genome and that EBERs seem to have antiapoptotic activity and also have the ability to induce the expression of interleukin-10 and thus promoting cell growth and survival [3, 9, 13]. In our patient BL cells were positive for EBER and the EBV-DNA PCR became negative after treatment, and so the case was considered a sporadic BL related to EBV infection.

Most patients with non-endemic BL present with peripheral lymphadenopathy or intraabdominal mass. Lymph node involvement is more common among adults than among children. The abdomen, especially the ileocecal area is the most common site of involvement; the ovaries, kidneys, omentum and other sites may be involved. Bilateral involvement of the breasts, as in our patient, may occur in association with puberty, pregnancy or lactation. The existence of B-symptoms (night sweats, weight loss or fever) is more frequent in BL than in other non-Hodgkin lymphomas [1, 6]. The disease is typically rapidly progressive and has the propensity to metastasize to CNS [1, 8].

Various staging systems have been proposed for anatomic staging in BL, but Ann Arbor and StJude/Murphy systems are the most used. During pregnancy CT scans are replaced by MRI to avoid radiation exposure to the fetus. Bone marrow aspiration and biopsy should be performed for every patient since it is frequent the presence of unexpected bone marrow involvement which has implications for treatment. Lumbar puncture is necessary for evaluation of CNS involvement [8]. BL, as other hematological malignancies, has the potential risk of maternal–fetal transmission of malignant cells. Pathological examination of the placenta should be undertaken, so that appropriate neonatal follow-up can be done [8].

BL is a very fast growing tumor and systemic chemotherapy is the treatment of choice for this aggressive disease in all its stages. There are several possible treatment protocols, all of them involving the use of intensive combination chemotherapy regimens incorporating administered high doses of cyclophosphamide. Prophylactic therapy to the CNS is mandatory and incorporated in all modern regimens. The overall survival rate of BL depends upon the stage of the disease at initial diagnosis—localized disease responds better and has higher survival rates than disseminated disease. Salvage therapy has been generally ineffective in patients failing initial treatment, emphasizing the importance of the initial treatment approach [8, 9].

The decision to use chemotherapy during pregnancy must be weighed against the effect of treatment delay on maternal survival. When possible, chemotherapy should be

postponed until the end of the first trimester. Unfortunately most pregnant women with non-Hodgkin lymphomas, including BL, have aggressive and advanced-stage disease, so starting chemotherapy should not be delayed.

The teratogenicity of any drug depends on the timing of exposure, the dose, and the characteristics affecting placental transfer. Due to ethical concerns, the best available data documenting effects of chemotherapy during pregnancy are derived primarily from case reports and limited retrospective studies.

Use of chemotherapy during first trimester increases the risk of spontaneous abortion, fetal death and major malformations. The fetus is especially vulnerable during the organogenesis period (from 2 to 8 weeks of gestation) and so, during this critical period, damage to any developing organ may lead to fetal death or to major malformation. First trimester exposure has been associated with a 10–20% risk of major malformation, with lower rates in single agent exposure (compared to combination regimens). After organogenesis, the eyes, the genitalia, the hematopoietic system and the CNS remain vulnerable to chemotherapy. Exposure during the second and third trimesters is not associated with malformations but increases the risk fetal and neonatal death, intrauterine growth restriction, preterm delivery, low birth weight and transient neonatal myelosuppression [5, 12, 14]. Several studies have focused on the neurodevelopment of children exposed to chemotherapy in utero and revealed no major impact in acquisition and development of cognitive capacities. Also current evidence suggests that children exposed to chemotherapy in utero have no increased long term risk of malignancies and infertility [2].

The majority of chemotherapeutic agents are classified as C or D based on the Food and Drug Administration pregnancy risk categories. Category C and D drugs were shown to have an adverse effect on the fetus in at least animal and/or human studies, respectively. Depending on the clinical case, the potential benefits of using these drugs to maximize maternal survival may sometimes outweigh the risk of fetal harm. A few agents, like methotrexate, are classified as category X (shown to cause fetal abnormalities or toxicity in animal or human studies), and so these drugs are not generally used as the risks are considered to outweigh any benefits.

Our case illustrates a sporadic case of BL associated with EBV infection with a second trimester diagnosis. According to Ann Arbor staging system this case was a BL stage IV (extra-nodal, bone marrow and breast, involvement). The chemotherapy regimen followed (French R-LMB protocol) included rituximab, cyclophosphamide, vincristine and methylprednisolone.

Cyclophosphamide and vincristine are D category drugs for use during pregnancy. Cyclophosphamide belongs to

the alkylating chemotherapy agents group. There are reports of several malformations after first trimester exposure to cyclophosphamide (including absent toes, eye abnormalities, low-set ears and cleft palate). On the other way, second and third trimester exposures are not associated with malformations but are linked to potential growth restriction and, possibly, neonatal pancytopenia. Vincristine is a vinca alkaloid agent. There are some sporadic references to vincristine first trimester exposure associated malformations (namely atrial septal defect and renal hypoplasia) as well as neonatal pancytopenia [5, 11]. In our case the newborn had adequate growth and no signs of myelosuppression despite the five days of chemotherapy.

On the other way, rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. This agent is C category for use during pregnancy. Animal studies revealed potential reversible fetal immunosuppression. A recent human study [7] demonstrated that fetal rituximab concentrations are higher than maternal concentrations, and also that, despite the complete absence of fetal B cells at birth, there was a rapid recovery without associated neonatal immune dysfunction, and authors concluded that rituximab can be an option for lymphoma treatment during pregnancy.

Conflict of interest statement None.

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