

# Extranodal Natural Killer/T-Cell Lymphoma of the Placenta: A Case Report of a Previously Undescribed Entity and Review of the Literature

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## Abstract

There have been only eight cases of non-Hodgkin's lymphoma with placental involvement published in the literature. Our case is the first case of NK/T-Cell lymphoma involving the placenta. NK and T-cells share a common ontogeny and both express T lineage antigens such as CD2 and CD7, but NK-cells lack surface CD3 and express cytoplasmic CD3 as well as CD16, CD56 and CD57. NK/T-cell lymphoma cells are infected with EBV and positive *in-situ* hybridization is considered a diagnostic requisite. High plasma EBV DNA is correlated negatively with survival and serial EBV plasma DNA monitoring is useful for assessing therapeutic response and detecting recurrence. There does not appear to be a clear relationship between placental involvement with systemic non-Hodgkin's lymphoma, nor a direct relationship of transplacental transmission if placental tissue is infiltrated with malignant cells.

**Keywords:** Non-Hodgkin's lymphoma; Natural killer cell lymphoma; T-Cell lymphoma; NK/T-cell lymphoma; Placental lymphoma; Epstein-Barr virus; Lymphoma in pregnancy

## Introduction

There have been only a few documented cases of non-Hodgkin's lymphoma with placental involvement published in the literature. We present the first case of Epstein Barr Virus positive, Natural Killer/T-cell lymphoma involving the placenta without fetal transmission and a review of the published cases with placental lymphoma. While the child in our case is disease free to date, the significance of lymphomatous placental infiltration and its effect on fetal outcome remains unclear due to the paucity of reported cases.

## Case Report

36 year old G5P4 Mexican female of 24 weeks gestation presented with a painful nodular swelling of the left upper extremity (LUE). She first noted a small nodule three months prior that progressed to a painful mass and ultimately ruptured four days before presentation. Examination revealed a 9cm erythematous exophytic mass with central ulceration and necrosis on the LUE and an additional Right Lower Extremity (RLE) indurated papule. No head or neck manifestations were noted and extensive ear, nose and throat evaluation was unremarkable. Complete blood counts demonstrated mild normocytic anemia with hemoglobin of 10.9 gm/dl, and normal differential counts. No abnormal cells were observed on peripheral blood smear. Blood biochemistries were normal.

Magnetic resonance imaging (MRI) of the LUE revealed two discrete soft tissue lesions. Index lesion was 7.2 × 2.8 × 8.4 cm, homogenous with low T1 and high T2 signal with superficial ulcerations, without evidence of vasculature. Additional smaller (1.2 × 2.5 × 3.0 cm) lesion was noted on the dorsolateral aspect of the elbow. The underlying muscles and fascia were not involved. A prominent axillary lymph node was present. MRI of the nasopharynx, sinuses, chest, abdomen and pelvis was normal.

A wide local excision of the LUE lesion and punch biopsy of the RLE lesion was performed. Paraffin embedded tissue was evaluated by light microscopy. Hematoxylin and eosin stained sections revealed conspicuous expansion of the dermis and subcutis by an atypical lymphoid infiltrate with no epidermotropism. Foci of angioinvasion and necrosis were noted. Immunohistochemical stains revealed that

the sheets of atypical cells expressed CD2, CD3, CD8 and CD56 but lacked CD4, CD5, CD20, and CD30. In addition, the tumor cells showed reduced CD7 expression. *In-situ* hybridization (ISH) for Epstein-Barr virus (EBV)-encoded RNA (EBER-1) was positive (Figure 1). Polymerase chain reaction (PCR) for T-cell receptor gene rearrangement was performed on tissue from the LUE lesion and detected a monoclonal population of T-cells (Figure 2). Whole blood EBV quantitative PCR revealed 738 copies/ml. Overall, the findings were diagnostic for EBV positive extranodal NK/T-cell lymphoma.

An iliac crest Bone Marrow (BM) aspirate and biopsy revealed normocellular BM containing maturing trilineage hematopoiesis with no morphologic evidence for involvement by lymphoma. A tandem flow cytometric analysis of the BM revealed no evidence of lymphoid monoclonality, aberrant antigen expression, or an increase in blasts. Routine cytogenetic studies showed a normal female karyotype. Based on the above findings a diagnosis was made of stage IV extranodal, EBV positive NK/T-cell lymphoma.

The patient continued with the pregnancy and was started on chemotherapy at 26 weeks gestation with Etoposide, Prednisone, Vincristine and Cyclophosphamide (EPOCH) without Adriamycin due to known P-glycoprotein resistance in NK/T-cells. At 36 weeks gestation she delivered a viable 2.5 kg boy with normal Apgar scores.

The placenta weighed 371 grams and measured 14 × 13 × 2 cm. The fetal surface was smooth, gray-blue with a radial distribution of distended vessels. The maternal surface was coarsely lobulated and velvety gray-red. Sectioning of the placenta revealed two dense fibrous areas of 0.5 and 2.0 cm diameter. Immunohistochemical analysis revealed a patchy intervillous atypical lymphocytic infiltrate with associated areas of infarct type necrosis. The infiltrate focally involved

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the fetal membranes, but no direct involvement of the chorionic villi was identified. Tumor cells expressed CD2, CD3 and CD8 but lacked CD20. Interestingly, the tumor cells were now CD30 positive. EBER-1 was markedly positive (Figure 1). T-cell receptor gene rearrangement was performed on placental tissue and again detected a monoclonal population (Figure 2).

One week postpartum, patient developed pain and swelling of her right second toe which was ultimately amputated and pathology revealed extensive involvement with the lymphoma. She was restarted on chemotherapy with prednisone, methotrexate, ifosfamide, L-asparaginase and etoposide (SMILE) and initially had excellent control of disease. After 4 cycles plasma, EBV PCR decreased from 22,947 copies/ml to <200 copies/ml with only a small residual lesion remaining on the LLE. A whole body Positron emission tomography/Computed tomography (PET/CT) showed no areas of suspicious metabolic activity. The residual LLE lesion was excised, and pathologic examination revealed no evidence of NK/T-cell lymphoma, suggesting a complete response to treatment. Since the patient was asymptomatic and disease-free, she was referred for stem cell transplant evaluation. However, this was not feasible for the patient.

One month later, the patient developed various new lesions on the upper and lower extremities, and a whole blood quantitative EBV PCR increased to 19,444 copies/ml. Chemotherapy with SMILE was reinitiated and quantitative EBV PCR became undetectable after two cycles of therapy. In total, she received six additional cycles of SMILE with excellent control of disease for seven months, until she developed progressive disease. Multiple lines of treatment were attempted including clinical trial, chemotherapy and local radiation but ultimately she developed diffuse subcutaneous lesions. After 29 months of extensive treatment with refractory disease and limited treatment options she entered hospice care and died shortly thereafter. Her baby boy is currently doing well at age four, meeting all of his age appropriate developmental milestones, and is free of malignancy.

## Discussion

NK-cells are large granular lymphocytes that function as cytolytic cells targeting tumor cells, bacteria, and virus infected cells. NK and T-cells share a common ontogeny and both express T lineage antigens such as CD2 and CD7, but NK-cells lack surface CD3 and express cytoplasmic CD3 as well as CD16, CD56 and CD57 [1].

NK/T-cell malignancies are uncommon diseases and are prevalent worldwide with a strong predilection for Asian, Central and South American populations. The World Health Organization recognizes two distinct entities: extranodal NK/T-cell lymphoma and aggressive NK-cell leukemia [2]. Common sites of involvement for extranodal include nose and upper aerodigestive tract, with involvement of the skin, salivary gland, testis, and gastrointestinal tract occurring less frequently. Rarely, NK/T-cell lymphoma can present fulminantly with widespread dissemination and involvement of the BM and peripheral blood [3].

The pathogenesis of NK/T-cell lymphoma remains ill-defined. The cells are invariably infected with EBV and positive *in-situ* hybridization is considered a diagnostic requisite. EBV is a ubiquitous herpes virus that infects preferentially B cells and occasionally other cell types, with a tropism toward epithelial. After primary infection, EBV establishes an asymptomatic latency state but can potentially develop into malignancy. Hematologic malignancies associated with EBV infection include Burkitt lymphoma, Hodgkin lymphoma, primary effusion lymphoma and NK/T-cell lymphoma. Epithelial tumors include nasopharyngeal

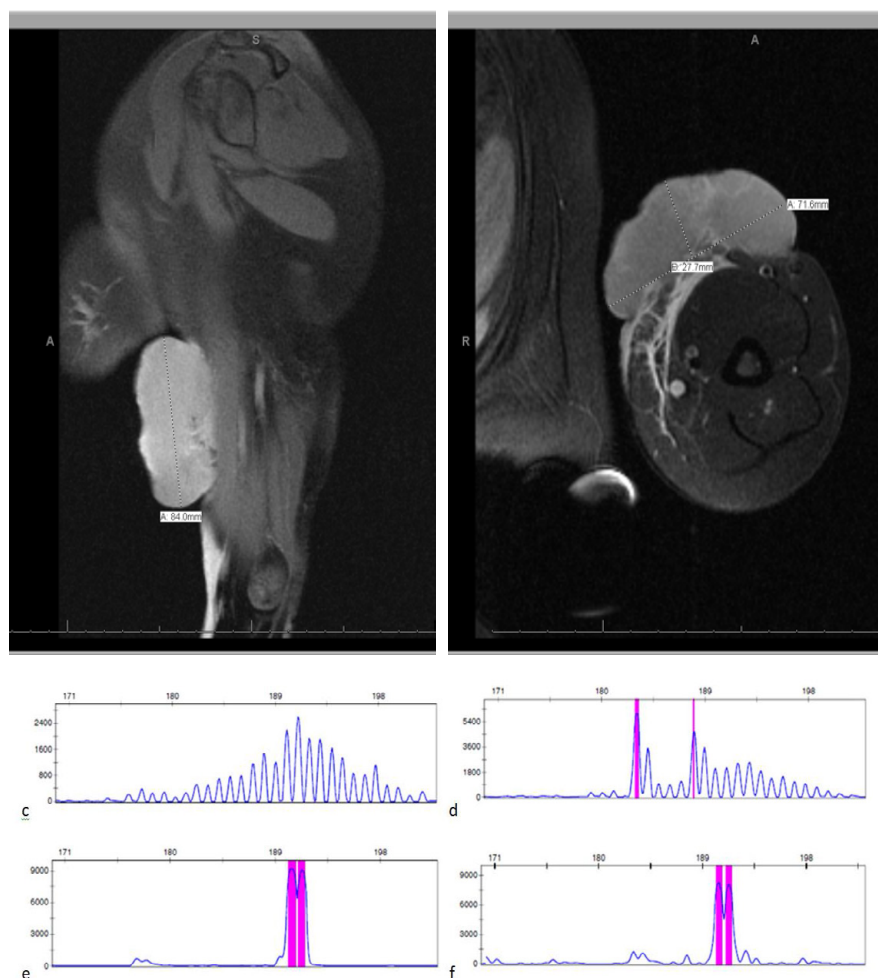
carcinoma and gastric cancer. In immunocompromised patients, reactivation of EBV infection is associated with post transplantation lymphoproliferative disorders. In patients with acquired immunodeficiency syndrome that develop lymphomas, EBV infection is found in about 30% of centroblastic and up to 90% of immunoblastic lymphomas [4].

The exact mechanism of malignant transformation remains undefined. It is known that when an EBV-positive lymphoma develops the virus progresses from polyclonal to monoclonal state. Analysis of the terminal repeat region of the EBV genome confirms the presence of a clonal episomal form. This infers that EBV is etiologically important and tumorigenic and not merely a bystander [5]. *In-situ* hybridization for EBER-1 accurately identifies infected cells in histopathologic sections and is informative in sites where EBV is usually absent, such as liver and bone marrow indicating lymphoma involvement. Quantification of plasma EBV DNA by PCR is prognostically relevant. Circulating EBV DNA is increased before treatment as proliferating tumor cells undergo apoptosis and release EBV genomic fragments into circulation. In addition, high plasma EBV DNA is correlated negatively with survival. In a study of 23 patients with NK-cell lymphoma, multivariate analysis including the presentation EBV DNA, stage, age and LDH level showed that presentation EBV DNA was the only significant factor, with a load of >6.1 X 10<sup>7</sup> copies/ml negatively impacting on disease free survival [6]. Failure to reach undetectable EBV DNA indicates a failure to reach complete remission which has an inferior prognosis. Serial EBV plasma DNA monitoring is useful for assessing therapeutic response and detecting recurrence [7].

For early stage NK/T-cell extranodal disease, chemotherapy and radiation is the main therapy with an expected cure rate of 70-80% [8]. NK-cells express high levels of P-glycoprotein resulting in a multidrug resistant (MDR) phenotype rendering standard anthracycline based regimens unsatisfactory. Combinations utilizing L-asparaginase (non-MDR) have shown improved survival. Chemotherapy alone is indicated for advanced NK/T-cell lymphoma and estimated 5-year OS is 52.3%. Aggressive NK-cell leukemia has a poorer outcome; median survival only 58 days. [9] Hematopoietic stem cell transplantation is considered [10].

Cancer in pregnancy is not uncommon with an estimated incidence of 1/1000 pregnancy [11]. Breast and cervical cancers are the most common primary malignancies encountered in pregnancy followed by leukemia, lymphoma, melanoma, and thyroid cancer. Dissemination to the Products of Conception (POC) typically occurs via transplacental hematogenous spread, but can be by lymphatic or direct invasion. The placenta is an organ of embryonic origin that nourishes the growing fetus by facilitating transfer of nutrients. It is not well understood how the allogenic fetus thrives and avoids immune rejection. Vertical transmission of cancer is rare, although maternal cells do reach the fetus. The placental barrier and the fetal immune system may serve to limit disease in the fetus but the exact mechanisms are unknown.

Cases of maternal malignancy with documented placental involvement are sparsely represented in the literature, perhaps due to failure to obtain placental pathology. In a review spanning 121 years by Dildy, there were only 53 cases of metastatic disease affecting the POC, and only 43 of the cases involved the placenta [12]. Breast and cervical cancer had the highest incidence of cancer in pregnant women but few reported cases with placental metastases. The most common cancer with placental metastasis was malignant melanoma. In fact, twelve of the 16 reported cases of melanoma to the POC reported involved the placenta. Lung was the next most common with six cases of placental



**Figure 1:** (a and b) Magnetic resonance imaging of the left upper extremity revealed two soft tissue lesions. A large left upper arm lesion  $7.2 \times 2.8 \times 8.4$  cm, mostly homogenous with low T1 and high T2 signal without vasculature but with superficial ulcerations and a smaller  $1.2 \times 2.5 \times 3.0$  cm lesion on dorsal lateral aspect of elbow with similar signal characteristics to larger lesion. The underlying muscles and fascia were not involved. (c-f) Multiplex PCR using analyte specific reagents to amplify the Vg(2-5, 8-11) J1+2+P regions of the TRG gene (Invivoscribe, San Diego, CA) and capillary electrophoresis was performed. (c) Negative control with Gaussian distribution of amplicons from a polyclonal T-cell population. (d) Positive control showing a 5% clonal T-cell population in a 95% polyclonal background. (e) NK/T-Cell Lymphoma cells from LUE lesion revealed a monoclonal population of T-cells. (f) NK/T-Cell Lymphoma cells from placenta revealed the same monoclonal population of T-cells.

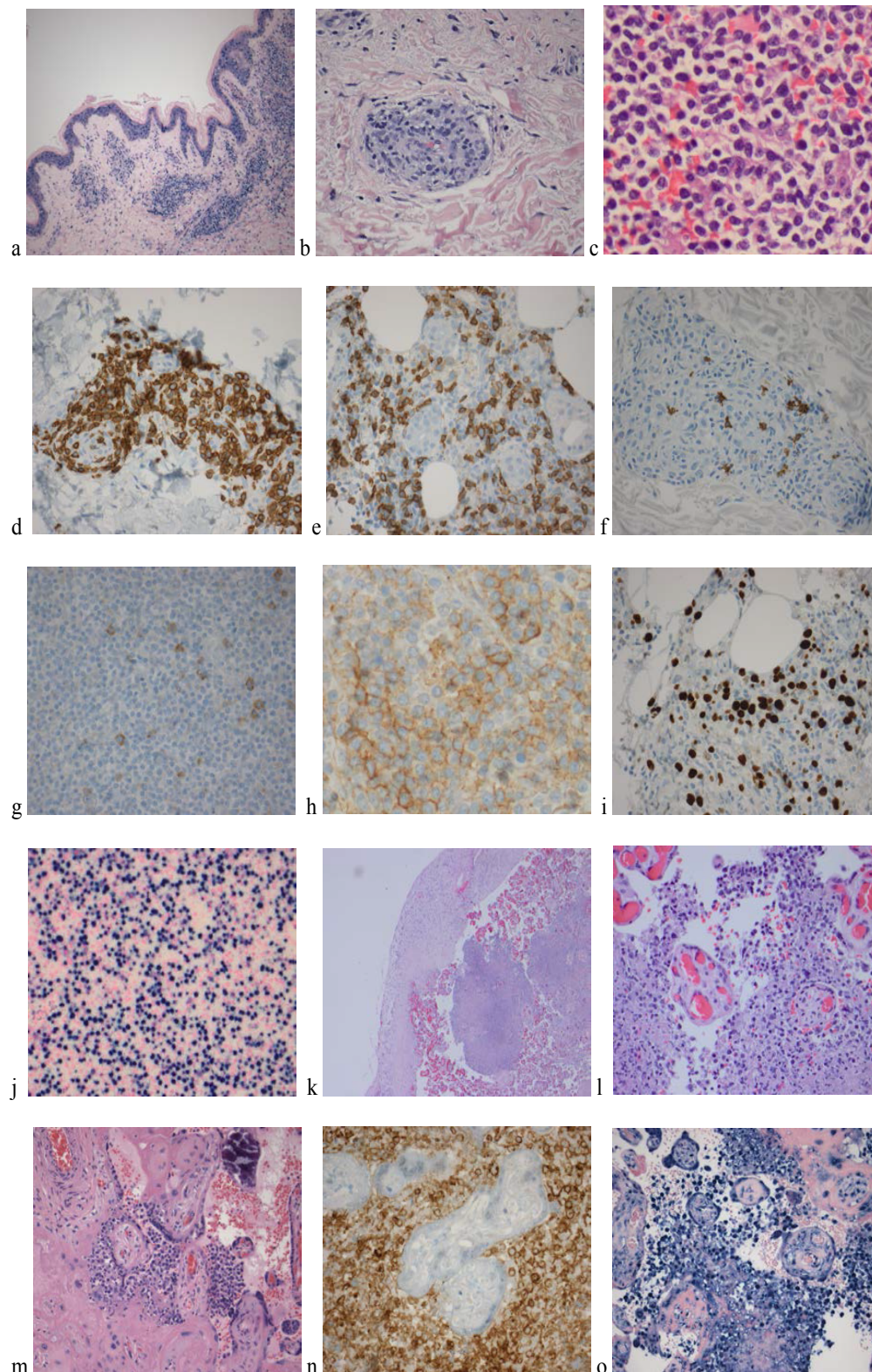
involvement, sarcoma with five and leukemia with four. Only one case of Hodgkin lymphoma with placental involvement was reported and one case of NHL with fetal transmission but no placental involvement.

The incidence of NHL during pregnancy is relatively low and reproductive organ involvement by NHL is even rare. Harowitz reported 121 patients from 1967 to 2011 with NHL during pregnancy [13]. Indolent lymphoma accounted for 5% of cases, aggressive lymphoma (diffuse large B-cell and peripheral T-cell lymphoma) for 48% of cases, and highly aggressive (Burkitt or immunoblastic) accounted for 47% of cases. No NK/T-cell lymphoma was reported in this study. Reproductive organ involvement (breast, ovary uterus and placenta) was reported in 53 of the 110 patients for whom involved organs were noted and most common in patients with Burkitt lymphoma, reported in 100% of endemic cases and 70% of non-endemic cases. None of the cases of Burkitt lymphoma had placental involvement.

Since 1986, there have been only six documented cases of placental involvement by NHL (Table 1). The first patient with a peripheral

immunoblastic T-cell lymphoma was treated with autologous stem cell transplant and in complete remission at the time of publication [14]. The second patient was diagnosed with immunoblastic B-cell lymphoma at delivery when the placenta was examined histologically [15]. The third patient, a 42 year old female, diagnosed with NHL in her second trimester and delivered at 26 weeks. Fetal autopsy was not performed and the mother died shortly thereafter from complications of lymphoma [16]. The fourth case, a 20 year old female, presented with an anaplastic large cell lymphoma at 27 weeks gestation [17]. Nishi reported a 30 year old with primary mediastinal B-cell lymphoma with placental involvement. The infant was reported to be healthy, but the mother died within a few months from progression of her lymphoma [18]. Lastly, Maruko reported a 29 year old with B-cell lymphoma that presented at 29 weeks. The disease was transmitted to the fetus and both mother and infant died a few months postpartum [19]. All of the cases reported placental involvement that was grossly visible and with intervillous space infiltration by tumor cells on microscopy, similarly to what was observed in our patient.





**Figure 2** Histopathology of NK/T-cell lymphoma involving the arm: **a** H&E stain, low power (100x), dermal infiltration by tumor lymphocytes without epidermotropism; **b** H&E stain, high power (400x), focus of angioinvasion and necrosis; **c** H&E stain, high power (400x), tumor infiltrate **d-j** Immunohistochemistry, high power (400x): **d** CD3 positive; **e** CD8 positive; **f** CD20 negative; **g** CD30 negative; **h** CD56 positive; **i** Ki-67 index 50%; **j** In situ hybridization for EBER-1 positive; **k-q** Histopathology of NK/T-Cell lymphoma cells involving placenta: **k** H&E stain, low power (100x), infiltration by tumor lymphocytes; **l** H&E stain, high power (400x); **m** H&E stain, high power (400x), tumor cells infiltrating intervillous spaces without invasion of chorionic villi; **n** CD30 positive (400x); **o** In situ hybridization for EBER-1 positive.

Author	Age	Gestation at presentation	Diagnosis	Placental IHC	Fetal disease	Maternal Outcome
Kurtin [14]	29, G3P2	40	Immunoblastic T-cell	CD3 (+), CD4(+),CD45(+), CD43(+), CD5(-), CD20(-), CD22(-)	Healthy	CR after transplant
Pollack [15]	33, G1P0	41.5	HIV/ Immunoblastic B-cell	CD20 (L26) (+),CD45 (+),	Healthy	Ongoing treatment at time of publication
Tsujimura [16]	42, G2P1	26	NHL	CD20 (L26) (+) CD43 (-), UCHL-1 (-)	Fetus died, no autopsy	Death 10 months
Meguerian [17]	20, G1P0	27	ALCL	CD30 (+), EMA (+) CD3(-), CD8(-),CD20 (-), CD56(-) t(2;5) (p23;q35)	Healthy	Healthy, at 11yr
Nishi [18]	30, G2P0	33	Primary Mediastinal, DLBCL	CD20(+), CD45(+) CD21(-), CD34(-), CD43(-), CD45(-)	Healthy, at 2yr	Death 1 month
Maruko [19]	29, G2P1	29	B-cell	CD20 (+), CD79a, CD3(-), CD4(-), CD8(-), CD56(-), CD30(-)	Death, 9 months	Death 5 months
Our Case	36, G5P4	24	NK/T-cell Lymphoma	CD2(+), CD3(+), CD8(+) CD56(+) CD4(-), CD5(-), CD20(-) EBER-1 (+)	Healthy, at 4yr	Death 2 years

**Table 1:** Case reports of Non-Hodgkin's lymphoma from maternal origin involving the placenta: Characteristics of patient, fetal transmission and survival. CR, complete remission; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large b-cell lymphoma; ALCL, anaplastic large cell lymphoma; IHC, Immunohistochemistry.

We report the first case of extra nodal NK/T-cell lymphoma with placental involvement. The fetal surface of the placenta was soft and gray-blue, whereas the maternal surface was coarsely lobulated, velvety gray-red that showed a nodular infiltrate positive for CD2, CD3, CD8, CD56 and interestingly the tumor cells in the placenta were CD30 positive. In situ hybridization for EBV was also positive. Despite extensive placental disease and fulminant maternal course, this case illustrates the possibility for an excellent fetal outcome. In fact, of the seven reported cases of placental involvement by NHL, including our case, only two offspring were affected with maternal disease.

Catlin et al. [20], reported transplacental transmission of NK-lymphoma in a 15 year old Thai woman (G1P0) that presented at 33 weeks gestation with mesosalpinx masses and BM infiltration. Tumor cells were positive for CD56 but negative for T-Cell markers including CD2, surface CD3 and CD8. The patient died on postpartum day 17, and the infant subsequently developed pancytopenia with BM involvement and died on the 59<sup>th</sup> day of life. Placental pathology was negative for lymphoma involvement. Scattered EBER-1 positive cells were only noted in the chorionic villi [20]. This case demonstrates transplacental transmission of NK-lymphoma with engraftment in the fetal bone marrow in a patient with systemic disease without placental involvement, but our case of NK/T-cell lymphoma has widespread EBER-1 positive cells in the placenta without transmission to the fetus (Table 2) It appears that the placenta itself may serve some sort of barrier function against malignant cells in addition to the fetal immune response. There are simply not enough reported cases to make concrete conclusions regarding fetal transmission. Some authors have speculated that factors such as Human Leukocyte Antigen (HLA) homozygosity, immunodeficiency of the fetus, or transmission during early gestation are at work in the rare cases with documented fetal transmission [20].

## Conclusion

There are only a few documented cases of non-Hodgkin lymphoma with placental involvement of malignant cells. We present the first case of NK/T-Cell lymphoma with placental involvement. Since there does not appear to be a clear relationship between placental involvement with systemic disease, nor a direct relationship of transplacental transmission if placental tissue is infiltrated with malignant cells, it is important to manage the mother until the time of delivery. We advocate pathologic examination of the placenta in pregnant women with lymphoma for evidence of placental involvement to help further clarify

	Our Case	Catlin, et al (20)
Diagnosis	NK/T-Cell Lymphoma	NK Cell Lymphoma
Age at Diagnosis	36 years	15 years
Week of Gestation at diagnosis	24 weeks	31 weeks
Reproductive History	Gravida 5, Para 4	Gravida 1, Para 0
Ethnicity	Mexican	Thai
Extranodal involvement Prior to delivery	Upper extremity soft tissue lesion	Bilateral Mesosalpinx Masses
Nodal Involvement Prior to delivery	Axillary lymph node	unknown
Bone Marrow involvement	No	Yes
Gestational Chemotherapy	Yes	No
Placenta Involvement	Yes	No
Fetal Disease	No (BM not performed)	Yes BM aspirate positive
Fetal Viability	Healthy Boy at 4 years	Boy, Death at 59 <sup>th</sup> day
CD2	+	+/-
CD3 surface	+	-
CD3 cytoplasmic	Not Tested	(+) mesosalpinx (-) bone marrow
CD5	-	-
CD8	+	-
CD10, CD19 and CD20	-	-
CD20	-	-
CD56	+	+
CD30	(-) Lymph node (+) placenta	-
EBER-1	+	+

**Table 2:** Comparison of our case of NK/T-Cell lymphoma with placental involvement and a case described by Caitlin et al. [20] of NK Cell lymphoma without placental involvement; Characteristics of patient including burden of disease, immunophenotype of lymphoma and fetal outcome are compared. EBER-1, *In-situ* hybridization for Epstein-Barr virus (EBV)-encoded RNA.

risk factors for transplacental transmission so a more clear relationship can be extrapolated.

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