

CASE REPORT

Possibilities and Difficulties of Treatment in the Case of a Pregnant Patient with Primary Mediastinal Large B-cell Lymphoma

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Background: There are several histologic variants and clinical subtypes of diffuse large B cell lymphoma, which includes the primary mediastinal large B cell lymphoma (PMBL). In the last 10 years the incidence of diffuse large lymphomas grew significantly.

Case report: We present the case and evolution of an aggressive life-threatening mediastinal B cell lymphoma with respiratory insufficiency, diagnosed in the 27th week of pregnancy. After 4 courses of R-CHOP the clinical status has somewhat improved, but the dyspnea, the facial and neck oedema and the trouble of speech persisted. After the patient was admitted to our hospital, she received DHAP regimen followed by mobilization with G-CSF. Before transplantation we administered another 3 courses of DHAP chemotherapy with spectacular results. We performed autologous hematopoietic stem cell transplantation preceded by BEAM chemotherapy. At present, 5 years post-transplant the patient is well, with no metabolically active disease on the PET-CT performed 3 months ago.

Conclusion: We can conclude that even in very complicated DLBCL cases, with a very good, efficient medical-team work we can salvage lives, in our case both of the mother and the child's. Even in partially chemo-refractory cases like in the presented one, salvage chemotherapy followed by autologous transplantation can lead to a successful treatment.

Keywords: primary mediastinal large B cell lymphoma, pregnancy, salvage chemotherapy, autologous stem cell transplantation

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Introduction

There are several histologic variants and clinical subtypes of diffuse large B cell lymphoma. Histologic variants include immunoblastic, centroblastic and anaplastic morphologies, whereas distinct clinical subtypes include primary mediastinal large B cell lymphoma (PMBL). In the last 10 years the incidence of diffuse large lymphomas, intravascular large B cell lymphoma and primary effusion lymphoma, grew significantly [1]. Lymphoma associated with pregnancy is uncommon, and there is relatively little information about the management and outcome of these cases. We considered important to present this difficult case with good outcome to show that even in aggressive large B cell lymphomas associated with pregnancy, with correctly conducted treatment there is the possibility of cure for the mother and of survival for the child.

Case report

We present the case of a 32 year old pregnant patient with primary mediastinal diffuse large B cell lymphoma. The disease started in the 3rd trimester, in her 27th week of pregnancy, with dyspnea and dry cough.

The general practitioner interpreted the fatigue and dyspnea due to the quite excessive weight gain of the patient, who weighed 107 kg at a height of 1.7 m.

The cough persisted and the dyspnea aggravated, this being interpreted by the general practitioner as a spastic bronchitis and antibiotics were given with no effect. Generalized pruritus and excessive night sweats appeared. The repeated medical examination revealed edema of the head and neck, and the accentuation of the collateral thoracic vein circulation.

Radiologic examination was postponed by the obstetrician and the general practitioner because of the pregnancy, but finally, due to her very severe clinical status, a chest X-ray was performed, which revealed a large mediastinal tumor mass. The patient was admitted to the hematological ward with the suspicion of mediastinal lymphoma in a very bad clinical condition with orthopnea, generalized pruritus, perspiration and irritative disabling cough.

The paraclinical examination revealed anemia with Hb 8.3 g/l, Hct 25.8%, normal white blood and platelet count, elevated ESR, with normal biochemistry. On the peripheral blood smear microcytosis and hypochromia could be observed. The bone marrow aspirates also showed deficit of maturation of the erythrocytes with only 10% of lymphocytes, without any other pathological findings.

Cardiac ultrasound was also performed, and it revealed a low quantity of pericardial effusion, the external compression of the right cardiac cavities and the infiltration and rigidity of the left ventricle.

The patient became very quickly O₂ dependent. The oxygen saturation without the administration of oxygen was 52.9%, elevating to 96% with permanent oxygen administration.

Prophylactic low molecular weight heparin and antibiotics were administered and she was transferred to thoracic surgery. Initially bronchoscopy was performed with very bad tolerance and it revealed the severe external compression of the trachea.

The emergency CT revealed a voluminous mediastinal tumor with compression on the trachea, esophagus and phrenic nerve. The tumor had the characteristic polycyclic contour, dislocating the trachea.

Fetal ultrasound was performed, which revealed the presence of normal fetal heartbeats, the fetus being 1000 ± 200 g and the pregnancy in the 27th week of evolution.

Due to the aggravated clinical condition, the low O₂ saturation and the very severe compressive syndrome, the patient was intubated. Transthoracic biopsy was performed and the histopathological examination confirmed the diagnosis of diffuse large B cell lymphoma.

In the 28th week of pregnancy a caesarian section was performed, and a female baby with an APGAR score of 6 was delivered, weighing 1340 g and measuring 35 cm. Immediately after delivery, chemotherapy was started for the patient with the classic R-CHOP protocol (Rituximab, Cyclophosphamide, Doxorubicin, Vincristin, methylprednisolone).

The status of the patient after delivery was extremely unstable. Bilateral chylothorax and left apical pneumothorax was diagnosed and 3 days post-delivery severe thrombotic complications appeared: thrombosis of the left subclavicular and left jugular vein. The first 4 courses of chemotherapy were administered in the intensive care unit. The patient's weight went down to 76 kg from 107. After 4 courses of chemotherapy, the clinical condition did not improve. She remained oxygen dependent with tracheostomy, high fever due to sepsis caused by methicillin resistant staphylococcus (MRSA), which responded to linezolid treatment.

The baby's evolution was favorable, being admitted to home care 2 months after delivery. Two weeks after the 4th course of R-CHOP chemotherapy the patient condition aggravated again, the bilateral chylothorax reappeared and the mediastinal compression aggravated.

At this stage, she was referred to our Bone Marrow Transplantation Unit from the Emergency Hospital in Sibiu for salvage chemotherapy, mobilization of hematopoietic stem cells and autologous transplantation. The response to DHAP (Cisplatin, Cytosar, dexametasone) salvage chemotherapy followed by G-CSF (granulocyte colony stimulating factor) administration was favorable.

The clinical condition improved, she became independent of oxygen therapy. We succeeded to mobilize a number of $6.0 \times 10^6/\text{kg}$ CD34+ cells, sufficient to perform the autologous hematopoietic stem cell transplantation. Before transplantation we administered another 3 courses of DHAP chemotherapy with spectacular results. The mediastinal mass diminished significantly and the chylothorax ceased.

We performed autologous hematopoietic stem cell transplantation, preceded by BEAM chemotherapy (Carbustinum, Etoposide, Cytosar, Melphalan). The transplant was well tolerated. Granulocyte recovery appeared in 10 days and platelet recovery in 15 days. In the period of aplasia the patient did not present any life-threatening complications (infections, bleeding). Post-transplant she benefited of antibiotic and antiviral and antifungal prophylaxis. Three months post-autologous transplant we performed a PET-CT examination, and due to the existence of a residual metabolically active mass of 2–3 cm in the mediastinum, we recommended radiotherapy and rituximab maintenance. At present, 5 years post-transplant the patient is well, has a healthy child and on the last PET-CT 3 months ago there was no evidence of the metabolically active disease.

Discussions

We considered important to present this difficult case of large B cell mediastinal lymphoma which appeared concomitantly with a pregnancy. The outcome of lymphoma cases associated with pregnancy depends on many factors. One of the most essential factors is the trimester of the pregnancy in which the lymphoma is diagnosed. If lymphoma appears in the first trimester, the pregnancy usually needs to be terminated and treatment started as soon as possible. This way the malformation of the fetus can be prevented and the mother can be saved. In the second trimester corticotherapy can be used to gain time until the fetus is viable. In the 3rd trimester chemotherapy can be started if necessary and the child must be delivered if possible. In the statistical analysis of 82 cases of lymphoma associated with pregnancy, the 3 years overall survival was 92% among those who started treatment during pregnancy, 83% among those who started treatment after delivery and 100% among those who terminated the pregnancy and started treatment immediately [2].

In our case the diagnosis was established in the 3rd trimester, the baby being delivered as soon as possible by caesarean section and the treatment was started immediately. The case presented many challenges, because it was the first pregnancy of a 32 year old woman who intended to keep her pregnancy in spite of the advice of the doctors and even at the cost of her own life.

One of the biggest challenges of this case was to be able to stabilize the mother with supportive intensive care, including mechanical ventilation until the child could be safely delivered. Another very important issue was the care of the neonate, who was delivered at 28 weeks with a very

small weight and an APGAR score of only 6. The professional care of the neonatologist made possible for the baby to survive and grow, to be today a healthy 5 year-old child.

Regarding chemotherapy, in cases of DLBCL the gold standard is R-CHOP 8 courses followed by rituximab maintenance [3]. Therapeutic response must be very carefully followed, because if after 4 courses we do not have good response to treatment, we must switch to so called "salvage" regimens like DHAP, ESHAP (Etoposid, Cisplatin, Cytosar, dexametasone) in the case of aggressive lymphomas [4]. Autologous hematopoietic stem cell transplantation is a very important modality of treatment and it can lead to cure of patients with DLBCL, as we presented in our clinical case [5,6].

In case of lymphomas, if the PET-CT examination shows residual adenopathies, patients should have involved field irradiation to prevent relapse [7]. If after radiotherapy a relapse still occurs, we should proceed to allogeneic hematopoietic stem cell transplantation. In the cases of patients with an HLA compatible sibling the situation is better and the transplant is rather well tolerated. In the lack of compatible family donors, donor search must be immediately started and if a compatible donor is found, allogeneic transplant must be performed. In the case of patients who are elderly or in a bad clinical condition, pre transplant conditioning can be a reduced intensity one, and these patients can benefit from the transplant and from its graft versus leukemia effect [8].

Conclusions

We can conclude that even in very complicated DLBCL cases, with a very good efficient medical-team work we can salvage lives, in our case both of the mother and the child's.

Lymphoma cases associated with pregnancy must be diagnosed in time, the histological and immunohistochemistry examination have to be very precise and accurate, in order to be able to treat the patient the best way possible. Each woman's situation is different, decisions about the best way to manage lymphoma diagnosed during pregnancy need to be individualized. Even in partially chemo-refractory cases like the presented one, salvage chemotherapy followed by autologous transplantation can lead to a successful treatment. Allogeneic transplantation from related or unrelated donors is another possibility for relapsed cases to salvage the lymphoma patients. Our case was presented to show that with the correct method of treatment we can obtain good pregnancy outcome, as well as good lymphoma outcome with the survival of the patient and the child.

References

1. Swerdlow S, Campo E, Harris N. WHO Classification of Tumours of hematopoietic and Lymphoid Tissues, 4th edition, Lyon, France, IARC Press, 2008.
2. Pereg D, Koren G, Lishner M. The treatment of Hodgkin's and non Hodgkin's lymphoma in pregnancy. *Hematologica*. 2007;92(09):1230-37.
3. Smith SM, Vose JM. Treatment approach to diffuse large B-cell lymphomas. In O'Brien S., Vose J.M., Kantarjian H.M. *Management of Hematologic Malignancies*. Cambridge University Press, 2011:286-307.
4. Baldissera RC, Nucci M, Vigorito AC. Frontline therapy with early intensification and autologous stem cell transplantation versus conventional chemotherapy in unselected high-risk, aggressive non-Hodgkin's lymphoma patients: a prospective randomized GEMO report. *Acta Haematol*. 2006;115:15-21.
5. Sieniawski M, Staak O, Glossmann JP. Rituximab added to an intensified salvage chemotherapy program followed by autologous stem cell transplantation improved the outcome in relapsed and refractory aggressive non-Hodgkin lymphoma. *Ann Hematol*. 2007;86:107-15.
6. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. *Blood*. 2007;110:3507-16.
7. Branson K, Chopra R, Kottaridis PD. Role of nonmyeloablative allogeneic stem-cell transplantation in patients with lymphoproliferative malignancies. *J Clin Oncol*. 2002;20:4022-31.