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【 CASE REPORT 】

Successful Management of Primary Mediastinal Large B-cell Lymphoma during Pregnancy

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Abstract:
We experienced a pregnant woman with superior vena cava syndrome at 15 weeks of pregnancy who was diagnosed with primary mediastinal large B-cell lymphoma and given chemotherapy. In this case, the clinical courses of both the mother and infant were favorable without any serious complications because of close multidisciplinary cooperation. Based on a retrospective review of this case, the administration of CHOP-like regimens during the second and third trimesters appears relatively safe. Because pregnancy and continuation of pregnancy are rare in patients with hematopoietic malignancies, the accumulation of detailed information is important.

Key words: primary mediastinal large B-cell lymphoma, pregnancy, superior vena cava syndrome, rituximab

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Introduction

Primary mediastinal large B-cell lymphoma (PMBL) is a subtype of diffuse large B-cell lymphoma (DLBCL) that proliferates mainly in the mediastinum and is regarded as an independent disease entity in the World Health Organization classification because of its characteristic clinical and pathological features (1). PMBL accounts for 2-3% of non-Hodgkin lymphoma cases in Europe and the United States (2) and for 0.35% overall and 1.0% in children and adolescents in Japan (3, 4). Its incidence may be lower in Japan than in Europe and the United States.

PMBL is a rare disease, accounting for <10% of DLBCL cases, and predominantly occurs in young women. PMBL often appears as a bulky mass arising from the mediastinum, and infiltrates the surrounding organs, causing pleural and pericardial effusion (5). In some cases, superior vena cava syndrome (SVCS) or phrenic nerve paralysis occurs (6). While there is a view supporting the avoidance of radiotherapy due to late complications, the efficacy of dose-adjusted (DA) etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R) chemotherapy (7) and usefulness of positron emission tomography (PET)/computed tomography (CT) after treatment have been discussed (8). PMBL has been attracting attention in recent years.

We herein report a pregnant woman with SVCS at 15 weeks of pregnancy who was diagnosed with PMBL and successfully received chemotherapy.

Case Report

The patient was a 28-year-old woman (gravida 2, para 1). Although she was a resident of another prefecture, she had been staying at her parents' house because of severe hyperemesis gravidarum for the past month before her visit to our hospital. Approximately 3 months earlier, she had developed a cough that persisted during her stay with her parents. Because respiratory distress appeared, she visited a neighborhood clinic. Venous engorgement in the precordia was detected, and chest radiography revealed a giant mass in the mediastinum (Fig. 1).

At 14 weeks of pregnancy, she was referred to our hospital. When she visited our hospital, she presented with orthopnea and respiratory distress. Her performance status (East-

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ern Cooperative Oncology Group) was 3, blood pressure 111/80, pulse rate 123 beats/min, respiratory rate 30 breaths/min, and oxygen saturation 98% (room air). Her respiratory sounds were clear, with no heart murmur. Blood tests results revealed no anemia; her lactate dehydrogenase level was 225 U/L, which was within the reference range, and her soluble interleukin-2 receptor level was slightly elevated to 564 U/mL. Furthermore, neither hepatic nor renal dysfunction was detected.

Chest CT revealed a mass measuring 11.0×5.2×8.7 cm that compressed the trachea, ascending aorta, and aortic arch (Fig. 2). To minimize radiation exposure, a CT-guided biopsy of the mass was performed. Histology (Fig. 3) showed medium to slightly large tumor cells located in a severe fibrotic lesion. On immunostaining, the tumor cells were positive for cluster of differentiation (CD) 20, negative for CD3, and partially and weakly positive for CD30 and paired box protein 5. Based on these findings, PMBL was diagnosed at 15 weeks of pregnancy. Because the patient presented with SVCS, the prompt administration of chemotherapy was essential.

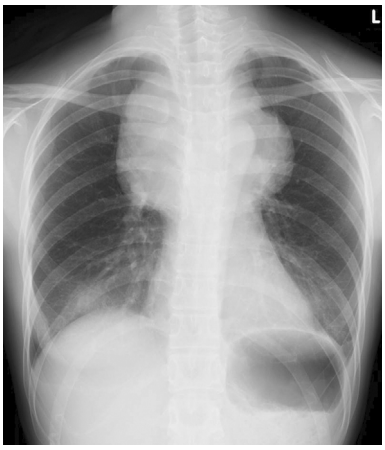

Figure 1. Chest radiography revealed a giant mass in the mediastinum.

While she did not wish to abort the pregnancy, chemotherapy was considered highly beneficial. After sufficient informed consent was obtained, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy was initiated on day 0 at 16 weeks of pregnancy. Although the mass initially reduced in size, the cytoreductive effect was slightly poor after completing three courses of CHOP chemotherapy. On day 0 at 25 weeks, rituximab was added; 3 courses of rituximab-CHOP (R-CHOP) chemotherapy were administered. She responded well to the treatment, which was temporarily discontinued at 31 weeks. The estimated fetal weight fluctuated within -1 standard deviation. Caesarean section scheduled at 36 weeks was postponed because Grade 4 (Common Terminology Criteria for Adverse Events Version 4.0) neutropenia was detected immediately before the procedure. Granulocyte colony-stimulating factors were administered, and we awaited an opportunity to perform the procedure. On day 1 at 36 weeks, labor pain developed, resulting in vaginal delivery. The patient delivered a female infant weighing 2,087 g with Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. The infant presented with transient tachypnea, requiring admission to the neonatal intensive-care unit (NICU) for mechanical ventilation. However, she was discharged without any apparent complications.

After the patient received 6 courses of a CHOP-like regimen, PET/CT confirmed complete metabolic remission (CMR). On postpartum day 13, DA EPOCH-R chemotherapy was initiated and was completed after 2 courses. No apparent adverse events were detected except for cytopenia.

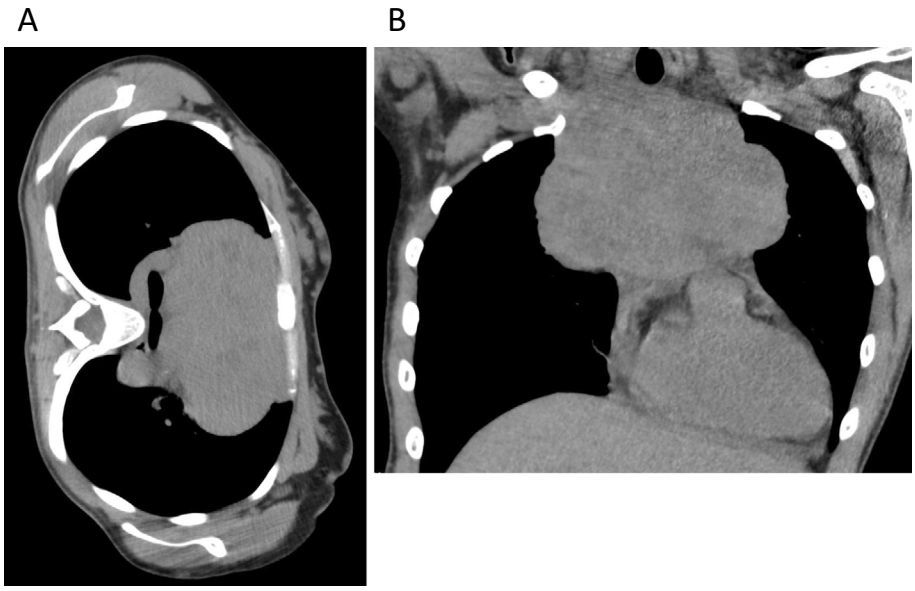

Figure 2. Chest computed tomography (A: sagittal section, B: coronal section) demonstrated a bulky mass in the anterior mediastinum measuring 11.0×5.2×8.7 cm compressing the bilateral main bronchi.

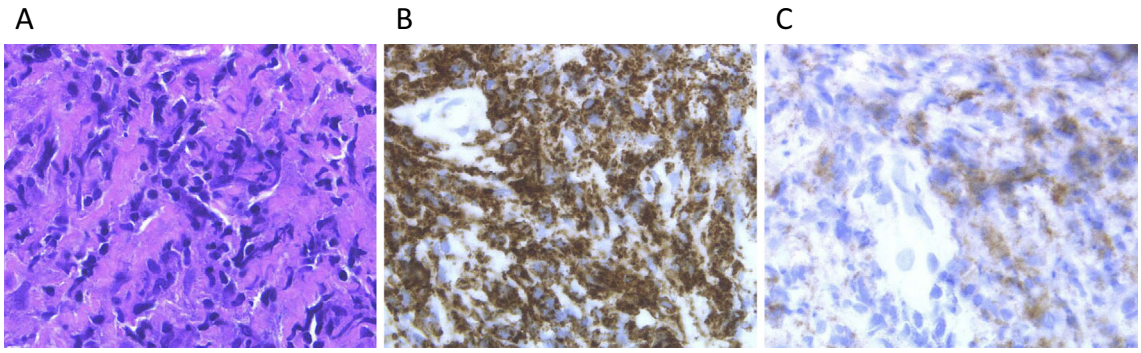

Figure 3. **Histology showed medium-sized to slightly large tumor cells located in a severe fibrotic lesion (A; Hematoxylin and Eosin staining ×400). On immunostaining, the tumor cells were positive for cluster of differentiation (CD) 20 (B; ×400) and partially and weakly positive for CD30 (C; ×400).**

Table 1. **Reported Cases of Primary Mediastinal Large B-cell Lymphoma Treated with Chemotherapy in Pregnancy.**

No. Reference	Age at diagnosis (year)	GA at diagnosis (weeks)	GA at start of treatment (weeks)	Pre-partum treatment	Pre-partum response	GA at delivery (weeks)	Mode of delivery	Post-partum treatment	Maternal outcome	Follow-up (months)	Neonatal outcome (Apger score)
1 [12]	22	13	13	R-CHOP	CR	34	VD	RT	CMR	20	Healthy (9/9)
2 [13]	35	30	30	R-CHOP	PR	36	VD	DA EPOCH-R	CMR	3	Healthy none
3 [14]	22	22	25	mPSL R-CHOP	PD	37	VD	RICE, ASCT RT	CMR	none	Healthy (8*)
4 Our case	28	15	16	CHOP R-CHOP	PR CR	36	VD	DA EPOCH-R	CMR	6	Healthy (7/8)

*Apger score of after 1 minute.

ASCT: autologous stem cell transplantation, CR: complete response, CMR: complete metabolic response, CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone, DA EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab, GA: gestational age, mPSL: methylprednisolone, No.: number, PD: progressive disease, PR: partial response, RT: radiation therapy, RICE: rituximab, ifosfamide, carboplatin, etoposide, R-CHOP: rituximab-CHOP, VD: vaginal delivery

Seven months after completing treatment, CMR has been maintained.

Discussion

The incidence of malignancy complicating pregnancy is approximately 1 per 1,000 pregnant women. The most common malignancy is breast cancer, followed by malignant melanoma, cervical carcinoma, and lymphoma (9). The incidence of hematopoietic malignancies complicating pregnancy is 0.02% in all pregnant women, with Hodgkin lymphoma accounting for approximately half of these malignancies (10). The incidence of non-Hodgkin lymphoma is reportedly 5.39 per 100,000 births (11). In cases of low-grade hematopoietic malignancies or those detected in the third trimester, some patients may be monitored without treatment until delivery. Thus, patients receiving chemotherapy during pregnancy are limited.

A PubMed search for English-language articles describing pregnant women with PMBL treated with chemotherapy revealed four cases, including ours (Table) (12-14). In many of these cases, patients received chemotherapy during the second trimester, presumably because they were symptomatic and could not remain untreated until delivery. In many recent cases, combination chemotherapy including rituximab was administered, achieving favorable therapeutic effects in all cases except one. The delivery route was vaginal in all cases, but a tendency of preterm delivery was detected. Because Caesarean section was not necessary in every case, it seems that the delivery route should be determined based on obstetric indications. With postpartum chemotherapy, disease control in the mothers was favorable. Although few detailed descriptions of the delivered infants are available, the infants in one case (13) and our own presented with transient tachypnea and required care in the NICU. In addition, our infant showed decreased B-cell counts (0.4% CD19 and 81.3% CD3 assessed by peripheral blood flow cytometry) and recovered after approximately 3 months. No apparent infection occurred during the infant's recovery.

In the guidelines for hematopoietic malignancy management (non-Hodgkin lymphoma) in pregnant women, there is no therapeutic strategy with strong evidence. The European Society for Medical Oncology Clinical Practice Guidelines (9) indicates that, given the high fetal malformation risk during the first trimester, pregnancy termination should be considered before chemotherapy. During the second and

third trimesters, CHOP chemotherapy is recommended. When delayed rituximab administration has the possibility of adversely affecting the maternal prognosis, rituximab administration is recommended if the potential effects on the fetal immune system are fully explained to the patient. The Management Guidelines From an International Consensus Meeting (10) recommend pregnancy termination or the initiation of chemotherapy during the first trimester and R-CHOP chemotherapy during the second and third trimesters, as that in nonpregnant women. However, the guidelines suggest that the indications should be carefully evaluated and determined due to the aforementioned rituximab effects on fetuses owing to placental transmission.

Regarding the general treatment approach of PMBL, the effectiveness of CHOP chemotherapy is limited, and retrospective studies in the pre-rituximab era suggest that outcomes with dose-dense chemotherapy, i.e., etoposide or methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (V/MACOP-B) chemotherapy are superior to those with CHOP chemotherapy (15, 16). In the post-rituximab era, a subgroup analysis of the Mabthera International Trial (17) compared patients with PMBL who were treated with CHOP-like chemotherapy with or without rituximab. R-CHOP chemotherapy showed a good complete remission rate and 3-year event-free survival rate, in contrast to CHOP chemotherapy, in patients <60 years of age with an age-adjusted International Prognostic Index score of 0 or 1. Seventy-three percent of patients received preplanned radiation therapy. Recently, support the avoidance of radiotherapy due to late complications. DA EPOCH-R chemotherapy, reported in 2013, demonstrated an excellent event-free survival and overall survival (7), and this treatment is considered the standard of care for PMBL in the United States; however, prospective multicenter studies are needed to validate the data (18).

Of the strategies mentioned above, the most appropriate therapy that can be adapted and is safe for pregnant women is unclear. It is true that DA EPOCH-R chemotherapy is excellent, but studies in mice have reported fetal cranial abnormalities and skeletal malformations due to etoposide, and there is insufficient evidence regarding the safety of this regimen in humans (19). Methotrexate is also considered to be highly teratogenic and should be avoided. In a previous study, rituximab was administered to 231 pregnant women, and outcomes were reported in 153 women, 90 of whom delivered live infants (20). In that study, the rate of spontaneous abortion during the first trimester was 21%, and that of preterm delivery was approximately 24%. Hematological abnormalities (e.g., lymphopenia mainly owing to a decreased B-cell count) were detected in 11 cases, and there were 4 cases of neonatal infection, 2 of fetal malformation, and 1 of fetal death. The incidence of these events was relatively low. Another report indicated that rituximab imposes a high risk of neonatal infection and should not be administered before delivery (21). In the present case, fortunately, severe infection did not occur but B-cell depletion was observed in the infant. We therefore feel that rituximab administration should be carefully considered, and continuous efforts should be made to accumulate more detailed reports.

Given the above, we consider CHOP or R-CHOP chemotherapy to be the first-choice treatment after patients in their second trimester. Furthermore, as with the findings of Fiascone et al. (13), we believe it best to administer DA EPOCH-R chemotherapy immediately after delivery. In our case, CHOP chemotherapy was initiated during the second trimester; however, as its effect was insufficient, rituximab was added. After delivery, DA EPOCH-R chemotherapy, which is reportedly effective, was administered, achieving a favorable response. Etoposide was administered in two courses, and rituximab was administered in five courses; whether or not this is sufficient remains unclear. However, the addition of rituximab and other anticancer agents, with the exception of anthracycline, must be further evaluated. The clinical courses of both the mother and infant were favorable without any serious complications, thanks to close multidisciplinary cooperation between the obstetric, pediatric, and other departments.

Although this study was a retrospective case-based review, CHOP-like regimens during the second and third trimesters appear relatively safe. Hematopoietic malignancy rarely occurs in pregnant women, and chemotherapy administration in pregnant women with hematopoietic malignancy is rare. Thus, the accumulation of detailed information regarding such cases, including details concerning the use of rituximab, will continue to be important in the future.

The authors state that they have no Conflict of Interest (COI).

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