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Superior vena cava syndrome related to mediastinal lymphoma in late pregnancy: A case report

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ABSTRACT

We report the initial diagnosis in a 28-year-old nulliparous woman of a primary mediastinal B-cell lymphoma in late pregnancy. For several weeks the patient had had symptoms of mediastinal obstruction, such as dyspnea, cough, swelling of the face and upper limbs. However, these symptoms had been misattributed to the pregnancy and a common cold. Due to a rapid decline in the patient's cardiovascular performance, she was transferred to the closest perinatal center in the 34th week of pregnancy, whereupon a cesarean section was performed. The diagnosis of a primary mediastinal B-cell lymphoma was made postpartum from a biopsy. This case emphasizes the importance of timely antenatal investigation in pregnant women with symptoms consistent with mediastinal obstruction. Thoracic ultrasonography can be a valuable tool for the detection of tumor-associated pleural and pericardial effusions.

1. Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a subtype of diffuse large B-cell lymphoma (DLBCL), accounting for 2–4% of non-Hodgkin lymphoma and up to 10% of DLBCL [1]. PMBCL has epidemiological, clinical, morphological and genetic features that differentiate it as a specific type of DLBCL [2]. PMBCL shares features with nodular sclerosis Hodgkin lymphoma, such as similar genetic patterns, immunological properties and a putative thymic B-cell origin [3,4].

PMBCL typically presents in female adolescents and young women. The clinical features are shown in Table 1. Its peak incidence is at 30–39 years of age, which is much younger than for other DLBCL subtypes [5]. Symptoms at diagnosis are caused by the bulky mediastinal tumor mass. While bone marrow infiltration is rare at initial diagnosis, disease recurrence often involves dissemination to extranodal sites (e.g. lung, kidney, gastrointestinal organs, brain) [6].

With progression of the lymphoma, infiltration of surrounding thoracic structures and compression of the airways and blood vessels may occur, resulting in superior vena cava syndrome [7]. The diagnosis of this syndrome is made on the clinical signs and symptoms of central venous obstruction, such as dyspnea, hoarseness, headache, chest pain and dysphagia. On physical examination many patients present with facial swelling, upper limb edema, venous distention in the neck and on the chest wall, cyanosis and a positive Pemberton's sign.

The present case highlights the importance of a comprehensive evaluation of pregnant women who present with clinical symptoms consistent with mediastinal obstruction. In our patient, superior vena cava syndrome presented by the patient was initially misattributed to the pregnancy. This delayed the diagnosis of the PMBCL.

2. Case History

In the 34th week of pregnancy, a 28-year-old Caucasian nulliparous woman experienced swelling of the face and neck, which soon spread to her arms. Apart from migraine and mild hypertension, her medical history was unremarkable. She interpreted these symptoms as pregnancy-related edemas, as she believed her legs were spared because she continuously wore anti-embolism stockings. Two weeks later she suffered from migraine, headaches, hoarseness, fits of coughing and mild shortness of breath. Her family doctor suspected a common cold, whereupon cough medicine and cold remedies were prescribed. Because of progressive respiratory distress in the 36th week of pregnancy, the patient presented at a municipal hospital, where echocardiography revealed pronounced left-sided pleural effusions, a concentric pericardial effusion of >4 cm and hepatosplenomegaly.

Due to rapid cardiorespiratory deterioration, the patient was immediately transferred to the local maternity clinic. She had elevated levels of CRP (6.4 mg/dL), GOT (60 U/L) and LDH (812 U/L), a leucocyte level of 15.7 G/L and a hemoglobin level of 12.1 g/dL, with a mean corpuscular

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Table 1
Clinical characteristics of primary mediastinal B-cell lymphoma (PMBCL).

Clinical features	
Median age	35 years
Female/male ratio	3:1
Mediastinal involvement	All
Superior vena cava syndrome	≈50%
Pleural and pericardial effusion	30–50%
Elevations of LDH – moderate to high	70–80%
B-symptoms (fever, night sweats, weight loss)	<20%
Bulky mediastinal tumor	70–80%

Adapted from [6,11]

volume of 78.6 fL. Due to the risk of imminent cardiovascular failure, a cesarean section was performed under epidural anesthesia, and backup with extracorporeal membrane oxygenation (ECMO) support. There were no complications and a healthy child was delivered. A biopsy of the mediastinal mass was taken at the time of surgery for cytological examination, which revealed cell-rich lymphocytic effusions with atypical cells (Fig. 1). Whole-blood flow-cytometric immunophenotyping and bone marrow examination gave no evidence of disseminated non-Hodgkin lymphoma.

A mediastinal tumor (16.4 × 11.2 cm) was demonstrated with 18F-FDG PET/CT imaging, showing compression of the main blood vessels and both lungs (Fig. 2 A). Suspecting a highly malignant mediastinal lymphoma, a multidisciplinary team initiated a dexamethasone-prephase treatment. The corticosteroid was later supplemented with cyclophosphamide, as the immunohistochemical examination of a CT-controlled biopsy rendered the final diagnosis of PMBCL. Large lymphoid cells with irregular nuclei stained up to 90% positive for markers CD20, CD79a, Bcl-2, Bcl-6 and Ki-67, whereas CD23, CD5 and cyclin D1 were negative. The lymphoma was defined as Ann Arbor stage IV due to striking infiltration of surrounding structures and malignant effusions. The international prognostic index (IPI), a clinical tool for predicting the outcome of non-Hodgkin lymphoma, was 4 (stage IV disease, elevated LDH, > 1 extranodal sites, ECOG 3 at initial diagnosis). Following recommendations, cerebral manifestations were excluded via MRI and cerebrospinal fluid cytology [8].

After one week of prophase treatment, which resulted in a distinct improvement of the patient's overall condition, R-CHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone) treatment was initiated. Methotrexate was not administered due to the presence of third-space fluids (in this particular case pleural and pericardial effusions), which are important contraindications. After the 6th cycle of chemotherapy, edema in the upper body had significantly declined, and follow-up PET-CT demonstrated considerable reduction of the tumor bulk (Deauville 3: fluorodeoxyglucose (FDG) uptake greater in the mediastinum but less in the liver) (Fig. 2 B). Because of repeated episodes of fever during chemotherapy-free intervals and the need for frequent blood transfusions, the etoposide dosage was reduced by a third. A multidisciplinary team decided on mediastinal radiation therapy after the 8th cycle of R-CHOEP. At the time of writing this case report six months after initial diagnosis the patient was still undergoing mediastinal radiation therapy.

3. Discussion

PMBCL is a distinct type of diffuse large B-cell lymphoma, which has been included in the 2016 revised WHO classification of lymphoid malignancies [1]. This subtype constitutes 6–10% of all DLBCL and is found more frequently in adolescent females and young women [9]. In particular, the annual incidence rate of PMBCL is 0.4 per million, with a peak between 30 and 39 years and female predominance (3:1 female to male) [10,11]. In up to 80% of the cases a bulky mediastinal tumor mass can be found, which may compress and infiltrate surrounding structures. In this regard, early dyspnea, dry coughing and other symptoms of superior vena cava syndrome are often described. Primary extranodal involvement and B-symptoms are less common at presentation [12].

We report a case where the symptoms of mediastinal compression were misattributed to the patient's late-stage pregnancy and a common cold, which delayed the diagnosis of PMBCL (Table 2). Our case has a striking similarity to that of a 28-year-old pregnant woman who presented with progressive cardiac failure at 30 weeks and who required immediate cesarean delivery [13].

The occurrence of lymphomas in pregnancy is reported to be rare (ranging from 1 in 1000 to 1 in 6000 deliveries) [12,14]. It is important to emphasize that pregnancy is associated with a plethora of physiological changes that can mask a pathological condition [15]. Pregnancy itself does not affect the natural course of the lymphoma, but it makes staging and therapy more complicated. Breast cancer, cervical cancer, Hodgkin disease, malignant melanoma and leukemia occur with a disproportionally high incidence in women of reproductive age and they are therefore the malignancies most frequently diagnosed during gestation [14].

About a dozen case reports have described the impact of pregnancy on the diagnosis and treatment of PMBCL [9,13,16–19]. Fiascone et al. point out that the diagnosis and need for chemotherapy during pregnancy do not preclude induction of labor and vaginal delivery at the scheduled date of birth [9]. Treatment options depend on the stage of pregnancy at which the lymphoma is discovered. For clinically unstable patients in late pregnancy, immediate delivery by cesarian section and

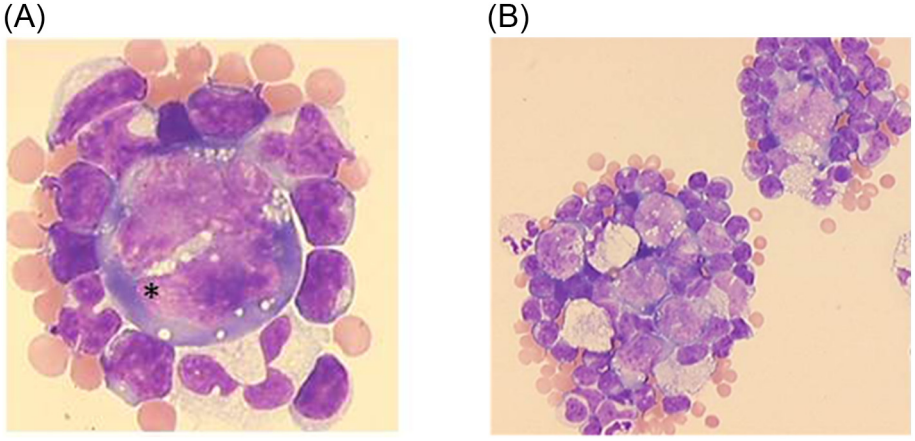

Fig. 1. Cytospin slide from pericardial effusion with a total cell count >6000/μl. Lymphocytic pleocytosis was shown together with 8% morphologically atypical cells that were indicative of non-Hodgkin lymphoma. A) Cell with morphological signs of malignancy (marked with an asterisk). B) Clustered atypical cells.

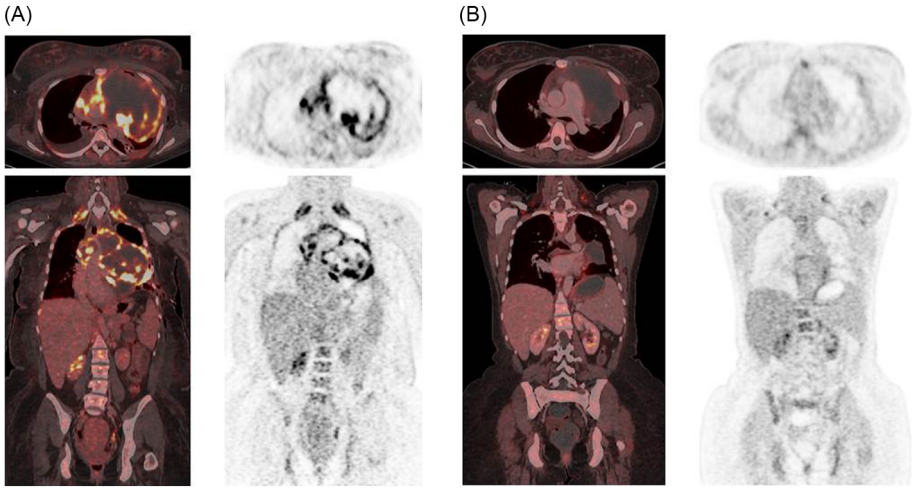

Fig. 2. 18F-FDG PET/CT imaging. A) Pre-treatment scan demonstrating a 16.4 × 11.2 cm mediastinal tumor mass with central necrotic areas and peripheral FDG enrichment. Obstruction and subtotal thrombosis of the superior vena cava and the left brachiocephalic vein, encasement of the aorta thoracica and subtotal compression atelectasis of the left lung lobe are shown. Pronounced signs of superior vena cava syndrome are evident with enlarged collateral venous vessels and pronounced liver congestion. B) Post-treatment response (Deauville 3). Reduction of mediastinal tumor mass and regression of subtotal thrombosis of the superior vena cava are evident.

postpartum CHOP-like chemotherapy is often the only therapeutic option. Depending on their overall condition, clinically stable patients can receive temporary corticosteroid treatment in late pregnancy until delivery, or an immediate and definitive treatment with R-CHOP chemotherapy [17]. Given that PMBCL is rare, there is a variation in clinical practice. Patients should be treated in specialized centers with multidisciplinary teams.

In conclusion, physicians must be alert and initiate appropriate antenatal investigation if obscure symptoms, such as dyspnea and swelling of the arms, are presented by a pregnant woman [20]. Reluctance to undergo appropriate radiological imaging during pregnancy is a significant pitfall in the diagnostic management of pregnant women, but thoracic ultrasonography is a useful initial alternative. The detection of tumor-associated pleural and pericardial effusions may indicate that the patient should receive further diagnostic workup, such as CT or MRI.

Contributors

ML Buchholtz contributed to the clinical and laboratory workup of the case and wrote the paper.

V Bücklein contributed to the clinical analysis of the case.

M Brendel performed the medical imaging.

M Paal contributed to the clinical and laboratory workup of the case and wrote the paper.

Table 2
Chronological order of events.

Gestational week	Clinical symptoms	Sequence of events
34th	• Swelling of face, neck and upper limbs	• Interpreted as pregnancy-related edemas
36th	• Exacerbation of migraine, hoarseness, coughing, mild shortness of breath	• Interpreted as common cold; prescription of cough medicine and cold remedies
Late 36th	• Progressive respiratory distress	• Presentation at hospital; sonographic detection of pleural and pericardial effusions
	• Fulminant deterioration of cardiorespiratory performance	• Transfer to maternity clinic, c-section
		• Diagnosis of PMBCL postpartum from biopsy of mediastinal tumor mass

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient consent.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Provenance and peer review.

This case report was peer reviewed.

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