Pulmonary alveolar microlithiasis and pregnancy: a case report and review of the other six cases in the literature

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ABSTRACT

Background: Pulmonary alveolar microlithiasis (PAM) is an inherited lung disease in which calcium phosphate deposits (chalcosphere) build up in the distal alveoli. There is no medical treatment for PAM, for patients with end-stage disease, lung transplantation is an option. Due to PAM is a rare condition with less than 1 per million prevalence, it becomes an exceptional case during pregnancy. We reported a pregnant PAM case and reviewed with other six cases in the-literature to date.

Case Presentation: A 21-year-old nulliparous pregnant woman with PAM presented in this report. The patient's obstetric and respiratory functions follow-up were unremarkable until 35 weeks of her gestation. Because of the patient had shortness of breath at 35 weeks of gestation, she was evaluated and hospitalized. She delivered by cesarean section at 38th gestational week.

Conclusion: It is still unknown that pregnancy how affect the women with PAM because the disease is rare. We reported a pregnant PAM case and reviewed with other six cases in the-literature to date.

Keywords: Calsinosis, lung disease, microliths and micronodular opacities, pregnancy, pulmonary alveolar microlithiasis, perinatal outcome.

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Background

Pulmonary alveolar microlithiasis (PAM) is an inherited lung disease in which calcium phosphate deposits (chalcosphere) build up in the distal alveoli. In patients with PAM, 16 different mutations in the type II sodium phosphate cotransporter, the type II sodium phosphate cotransporter (NPT2b), have been reported. There is a familial autosomal recessive inheritance pattern about one-third of cases, but mostly are sporadic [1]. Patients are generally young and asymptomatic; however, the disease is diagnosed with lung imaging methods taken for other purposes [2]. PAM starts with mild dyspnea and progresses slowly; desaturation occurs in young adulthood and respiratory insufficiency occurs in late middle ages. Explosive onset and rapid progression can be seen in infants and children. There is no medical treatment for PAM, instead the treatment is based on the symptoms. For patients with end-stage disease, lung transplantation is an option [3,4].

Because of PAM is a rare condition with less than 1 per million prevalence [5], it becomes an exceptional case during pregnancy. We reported a pregnant PAM case and reviewed with other six cases in the literature to date.

Case Presentation

A 21-year-old nulliparous pregnant woman admitted to Umraniye Training and Research Hospital, Obstetrics and gynecology clinic (Istanbul, Turkey), at 14 weeks of her gestation.

The patient reported having had dyspnea in her medical history since she was 7 years old. At that time, biopsy had performed, and she had diagnosed with PAM. There was no similar disease history in her family. Figure 1 shows the notable diffusely distributed calcified nodules on the computed tomography scan when she was 17 years old. She had examined regularly at the respiratory medicine clinic once a year. It was learned from patient's history that her pregnancy was unplanned and that her disease did not progress aggressively before pregnancy and that she used inhaler bronchodilator and methylprednisolone only when needed and that she did not use regular medication. After she got pregnant, she was examined in the respiratory clinic twice, at the 17th week and at the 28th week. The patient was examined by an obstetrician monthly between 14th and 28th weeks of her pregnancy, and then she was examined every 2 weeks. During this follow -up period,

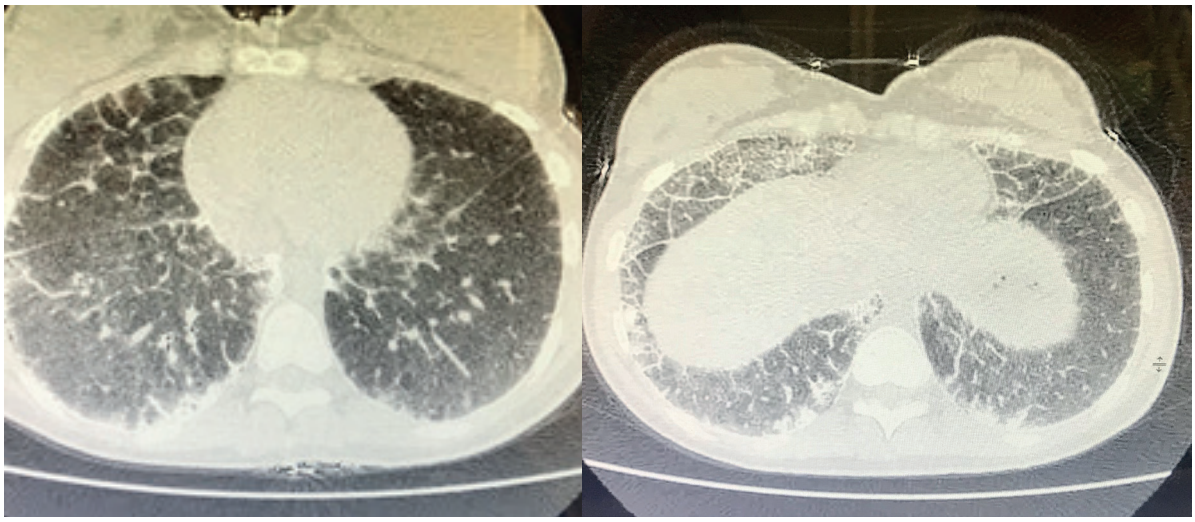

Figure 1. *The computed tomography scan shows multiple calsified micro nodules that scanned when she was 17 years old.*

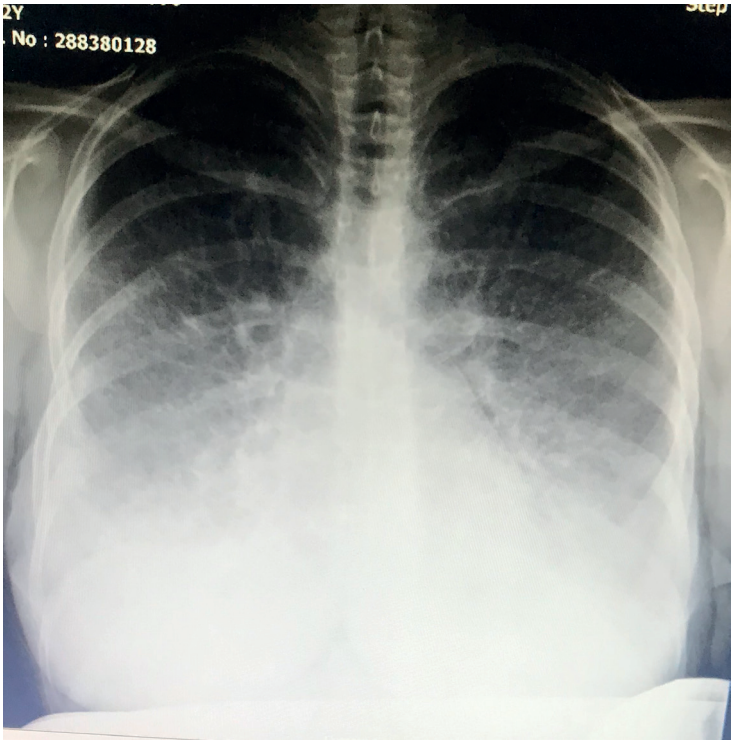

Figure 2*. Posterior anterior chest radiography: bilateral diffuse calcified micronodular views at 35 weeks of the patient's gestation.*

the patient's vital signs were evaluated by physical examination, such as blood pressure measurement, pulse measurement and pulmonary auscultation. Her hematological parameters, liver profile, and urine report showed within normal range. She did not have any obstetric or respiratory complaints until the 35th gestational week. Because of the patient had shortness of breath at 35 weeks of gestation, she was hospitalized in perinatology clinic. There were fine crackles in both lower lung areas as a pulmonary auscultation finding and the chest X-ray showed bilateral calcified micro nodules (Figure 2). Her pulmonary function tests were showed: forced expiratory volume in one second (FEV1) 2.98 l (4.12 l predicted), forced vital capacity (FVC) 3.42 l, FEV1/FVC 73.6% (84.4% predicted). In the obstetric ultrasonography, the fetal heartbeat was positive. The amniotic fluid was at normal level. The estimated fetal weight was found 2,597 g in accordance with 55th percentile. In the non-stress test examination, the fetal heartbeats were reactive and there was no uterine contraction. Umbilical artery Doppler was not pathological. Since the patient's respiratory complaints persisted, consultations were made to the department of cardiology and respiratory medicine clinics. Primary cardiac pathology was not observed but the respiratory medicine specialist recommended to use 100 mg of salbutamol sulfate; inhaler and 3 times a day, 0.25 mg/ml budesonide; with

nebules twice a day, ipratropium bromide; 0.5 mg twice daily with nebules. Respiratory medicine specialist also suggested that if pregnancy will be terminated by cesarean section, spinal anesthesia should be preferred and, 40 mg of methylprednisolone should be given 1 day before and 1 day after the operation intravenously.

The patient, whose clinical symptoms decreased, was discharged 1 week after the hospitalization. When the patient came to the 37th week, she applied to us with complaints of dyspnea and syncope. She was hospitalized again. The blood gas analysis results were as follows: pH, 7.47; arterial carbon dioxide tension, 26.3 mmHg; arterial oxygen saturation, 100%; and bicarbonate, 21.8 mEq/l. She did not have any syncope attack during her hospitalization. However, she stated that she had syncope 2-3 times a week at home. Upon this, she was consulted with the neurology and psychiatry clinic, but neuropsychiatric pathology was not observed. It was decided by maternal-fetal medicine specialists terminate the pregnancy with vaginal delivery at the 38th week and the patient should be hospitalized until the delivery. Labor induction with prostoglandin E2 ovul was started when she reached 38 weeks of gestation. However, 24 hours later, due to unsuccessful labor induction, the cesarean section was decided; and 40 mg of methylprednisolone treatment was given preoperatively. Caesarean section was performed with spinal anesthesia. 3,005 g baby girl was born. The baby's 1st minute Apgar score was 9, and the 5th minute Apgar score was 10. 40 mg of methylprednisolone treatment continued on the postoperative first day. No respiratory distress or any other lung pathology was observed in the baby in the first 4 months. After the patient was discharged, shortness of breath continued for the first 2 months, but there was no additional recommendation from the respiratory medicine specialist.

Discussion

PAM is a lung disease characterized by the interalveolar accumulation of calcium phosphate microliths. Mutation of the SLC34A2 gene encoding a type IIb sodium-dependent phosphate co-carrier causes an accumulation of alveolar microliths. Generally, familial predisposition is observed at the disease. It is diagnosed up to the age of 40. The frequency of the disease is equal in men and women and PAM disease can be observed all over the world, but it is more common in Turkey, followed by China, Japan, India, Italy, and the USA [6]. PAM is a disease that progresses insidiously, it starts asymptomatic, and may worsen over time and progress to the pulmonary fibrosis, respiratory failure and core pulmonale. There is no medical or surgical treatment yet, but lung transplantation is an option.

Table 1. *Summary of the pregnancy case reports with pulmonary alveolar microlithiasis in the literature.*

CASES	AGE	PAM HISTORY	PULMONARY FUNCTION TESTS	OBSTETRIC OUTCOME
1) Abba [7], Kingdom of Saudi Arabia	37	Family history, asymptomatic during pregnancy	(FEV1) 3.6 l (90% predicted), (FVC) 3.8 l, FEV1/FVC 94.7% (DLCO) was 82% predicted.	Placenta previa as the cause of antepartum hemorrhage. When she was 8 months pregnant delivered by cesarean section
2) Rodriguez et al. [8], Uruguay	36	Sporadic, diagnosed during unrecognized pregnancy	N/A	Become symptomatic at 34th week, delivered at 38th week by cesarean section, died after 4 months of puerperium cause of the progressive restrictive deterioration
3) Souzo Filho et al. [9], Brazil	26	Sporadic, diagnosed 10 months before pregnancy	(FVC), 2.80 l (25.9% of predicted); (FEV1), 2.59 l (13.9% of predicted); FEV1 / FVC ratio, 91.1% (75.6% of predicted); and forced expiratory flow between 25% and 75% of FVC, 3.63 l/second (65% of predicted)[a]	Become symptomatic around 28 weeks, delivered at 32th week by cesarean section
4) Erdem et al. [10], Turkey	36	Sporadic, diagnosed 4 years before pregnancy	N/A	Worsening occurred at second and third trimester. Delivered at 31th week by cesarean section due to unstoppable preterm labor
5) Sethy et al. [11], India	27	Sporadic, diagnosed 1 week after delivery	Spirometry showed mild restriction and DLCO was 48% predicted.	Become symptomatic around second trimester, delivered full term baby, vaginally
6) Aktürk et al. [12], Turkey	37	Undetermined family history, diagnosed 5 years before pregnancy	N/A	Become symptomatic around 35 weeks, delivered preterm baby by cesarean section
7) Present case	21	Sporadic, diagnosed before pregnancy	(FEV1) 2.98 l (4.12 l predicted), FVC 3.42 l, FEV1/FVC 73.6% (84.4% predicted)	Become symptomatic after 35th week, delivered at 38th week by cesarean section due to unsuccessfully labor induction

FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; DLCO: Diffusion capacity for carbon monoxide.
[a] 1 year and 8 months after delivery.

We searched including the following "pulmonary alveolar microlithiasis" and "pregnancy" words in PubMed and Google Scholar in October 2020. There are very few cases with PAM in pregnancy reported in world literatures until now [7-12].

We summarized these only seven cases in Table 1. In this case, we observed the effects and results of PAM on mother and fetus at 14-38 weeks of pregnancy. Our case had a typical evolution. There was no change in the existing complaints at first and second trimesters, respiratory complaints worsened in the third trimester. The fetus has completed its development and was born healthy at 38 weeks. In the other, six cases reported a vaginally delivery. The indications of cesarean delivery were usually associated with obstetric reasons. Rodriguez et al. [8] reported a case that occurred death cause of severe restrictive pulmonary disease at fourth month after delivery while waiting for lung transplantation. All fetuses were born alive and with appropriate weight for gestational age.

Respiratory functions of almost all pregnant cases with PAM worsened in third trimester. This can be explained by the enlargement of uterus displaces the diaphragm upwards which causes a reduction in the respiratory functions and lung capacity. The total pulmonary resistance may be decreased due to relaxation of the tracheobronchial smooth muscle under progesterone effect [13].

The respiratory function test showed us a mild degree restrictive pulmonary disease in our patient at 35 weeks of her gestation. As is known from other more common diseases with interstitial pulmonary fibrosis, the morbidity and mortality are correlated to the pre-pregnancy pulmonary functional tests. In another case report from Turkey [10] although the patient had no complaint of dyspnea in her first pregnancy when younger, presented with restrictive type pulmonary function tests and had preterm delivery in her second pregnancy. In restrictive type pulmonary disease, the total exhaled volume, known as the FVC, if greater than 50%, the pregnancy tends to be uneventful as in our patient [14]. Because of the rarity of the PAM cases with pregnancy, the management protocol for these patients is still uncertain. If the patient presents in early pregnancy, the clinicians should evaluate the patient that whether medical termination of pregnancy can be an option or pregnancy should be allowed.

Currently there is no definitive therapy for the treatment of PAM. In the previous reports steroids, bronchoalveolar lavage, calcium chelating agents, and disodium etidronate have demonstrated with mixed results [1]. Unfortunately, the long-term prognosis is poor and 34.1%-42.9% of patients died within 10-49 years of diagnosis, at a mean age of 46.2 years. Unilateral or bilateral lung transplantation had been reported as only effective therapy [15]. Infertility cases have been described in males associated deposition of microliths in testicles and seminal vesicles [15]. Although there is a risk of infertility due to deposition of the microliths in the ovaries, these patients can conceive.

Conclusion

As a result, it is still unknown that pregnancy how affect the women with PAM because the disease is rare. Rapid progression of the disease is not shown in the pregnant cases that we reviewed but it is possible cause of conditions which alter pulmonary functions. It seems that respiratory functions were also poor before and during pregnancy in the case with rapid progression after birth and resulting death [8]. In three cases occurred preterm delivery one of them associated with unstoppable uterine contractions, others iatrogenic due to maternal clinical deterioration. Abortion, in utero excitus, fetal growth restriction and fetal distress have not been reported yet.

Close follow-up for possible rapid deterioration should be provided for the pregnant patients with PAM. It is important to assess the risk of each patient ideally pre-pregnancy. Pregnancy is advised against if there is severe pulmonary restriction or if pulmonary hypertension is present. Management includes multidisciplinary input from the respiratory physician and obstetrician.

What is new?

Due to PAM is a rare condition with less than 1 per million prevalence, it becomes an exceptional case during pregnancy. There are only six case reports in the literature to date. It is still unknown that pregnancy how affect the women with PAM because the disease is rare. The authors wanted to contribute to the literature by presenting this rare case.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

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Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 21
2	**Final diagnosis**	PAM with pregnancy
3	**Symptoms**	shortness of breath
4	**Medications**	Methylprednisolone
5	**Clinical procedure**	Cesarean section
6	**Specialty**	Obstetrics, respiratory medicine