BILATERAL CHANGES IN THE LUNGS OF A PREGNANT WOMAN CAUSED BY BILATERAL SPONTANEOUS PNEUMOTHORAX

Jelena Radojčić¹, Jelena Marković², Željko Garabinović³, Milan Savić^{3,4}, Jelena Stojšić²

¹City Institute for Urgent Medical Care, Belgrade, Serbia

²Service of Pathology, Clinical Center of Serbia, Belgrade, Serbia

³Clinic of Thoracic Surgery, Clinical Center of Serbia, Belgrade, Serbia

⁴Faculty of Medicine, University of Belgrade, Belgrade, Serbia

BILATERALNE PROMENE U PLUĆIMA TRUDNICE IZAZVANE BILATERALNIM SPONTANIM PNEUMOTORAKSOM

Jelena Radojčić¹, Jelena Marković², Željko Garabinović³, Milan Savić^{3,4}, Jelena Stojšić²

¹Gradski institut za hitnu medicinsku negu, Beograd, Srbija

²Služba za patologiju, Klinički centar Srbije, Beograd, Srbija

³Klinika za torakalnu hirurgiju, Klinički centar Srbije, Beograd, Srbija

⁴Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare disease that most commonly affects women of reproductive age. The disease is manifested by diffuse destruction of the pulmonary parenchyma with the formation of cysts on a characteristic finding of multidetector computerized tomography (MD-CT) of the chest. It is thought that the presence of cells with estrogen and progesterone receptors among proliferating smooth muscle cells lead to the spread of cystic structures lined by endothelial cells. Towards the end of pregnancy and after childbirth, collapse of the lung parenchyma or rupture of the cyst wall occurs causing a dramatic clinical picture in the form of pneumothorax. Sirolimus is the only drug of choice that should improve and stabilize the patient's pulmonary function and quality of life. Unfortunately, this drug is not always effective enough, so only option for treatment is bilateral lung transplantation.

The authors present the patient in the last trimester of pregnancy who was admitted to the hospital with clinical picture of bilateral spontaneous pneumothorax. Dramatic picture of pneumothorax could not be solved solely by drainage in which atypical segmental resection of the lung was performed within a few days so on these samples lymphangioleiomyomatosis were diagnosed.

Keywords: *lymphangioleiomyomatosis, pneumothorax, pregnancy, dysregulation of estrogen receptor, dysregulation of progesterone receptor, proliferation of smooth muscle, lymphangiectasia, proliferation of HBM-45 cells.*

SAŽETAK

Limfangioleiomiomatoza (LAM) je retko oboljenje koje najčešće zahvata žene u reproduktivnom periodu života. Bolest se manifestuje difuznom destrukcijom plućnog parenhima sa stvaranjem cisti na karakterističnom nalazu multidektor kompjuterizovanom tomografijom (MD-CT) grudnog koša. Smatra se da prisustvo ćelija sa estrogen i progesteron receptima među proliferisanim glatkomišićnim ćelijama dovodi do širenja cističnih struktura obloženih endotelnim ćelijama. Pred kraj trudnoće i posle porođaja dolazi do kolapsa parenhima ili rupture zida ciste uzrokujući dramatičnu kliničku sliku u vidu pneumotoraksa. Sirolimus je jedini lek izbora koji treba da poboljša i stabilizuje plućnu funkciju i kvalitet života pacijenta. Na žalost, ovaj lek nije uvek dovoljno efikasan, pa je jedina mogućnost za lečenje obostrana transplantacija pluća.

Autori prezentuju pacijentkinju u poslednjem trimestru trudnoće koja je u bolnicu primljena sa obostranom slikom spontanog pneumotoraksa. Dramatična slika pneumotoraksa nije mogla biti rešena samo drenažom kod koje je u roku od nekoliko dana izvršena atipična segmentalna resekcija pluća, pa je na tim uzorcima postavljena dijagnoza limfangioleiomiomatoze.

Ključne reči: *limfangioleiomiomatoza, pneumotoraks, trudnoća, disregulacija estrogen receptora, disregulacija progesteron receptora, glatkomišićna proliferacija, limfangiektazije, proliferacija HBM-45 ćelija.*

INTRODUCTION

The diagnosis of rare lung tumors is a challenge. Some rare lung tumors are diagnosed only once during the years of practicing pulmonary pathology and that only in highly specialized hospitals exclusively dealing with thoracic surgery. According to the latest WHO classification, lymphangioleiomyomatosis (LAM) belongs to the group of mesenchymal tumors, subgroup of PEComatous tumors. In the literature, LAM has been described as a tumor associated with tuberous sclerosis. Pneumothorax and acute respiratory distress syndrome are the leading symptoms of LAM [1, 2]. The literature describes patients who have been diagnosed with LAM in pregnancy and who have had to have a premature birth [3, 4]. Radiological findings as well as pathohistological, morphological and immunohistochemical findings were characteristic of LAM [5].

We present a patient who developed bilateral spontaneous pneumothorax in the last trimester of pregnancy.

CASE REPORT

We present a case of 32-year-old pregnant woman and non-smoker who was hospitalized at the Clinic for Thoracic Surgery Clinic of the Clinical Center of Serbia, Belgrade, Serbia, in February 2020 for bilateral chest pain and shortness of breath. Because of suspicion to bilateral spontaneous pneumothorax after reviewing radiological findings, it was performed multidetector -computed tomography (MD-CT). MD- CT cross-sectional imaging has determined bilateral diffuse cystic changes of thin and smooth wall both directly below the pleura and deep within the lung parenchyma [Figure 1a, 1b]. It was concluded that reexpansion of the pulmonary parenchyma could not be solved only by bilateral drainage but only by surgical procedure.

In order to perform surgery, c-section performed in 37th week of pregnancy at the Clinic for Gynecology and Obstetrics of the Clinical Center of Serbia in Belgrade, was necessary. Thereafter, it was performed atypical segmental resection on the left lung and after a few days, resection of the same type to the right lung.

Pathological findings:

One day before macroscopic examination and sampling, insufflation of 10% buffered formalin was performed in order to make easier examination of distended alveolar spaces by imitating inspiration.

Macroscopic finding: Routine macroscopical examination of sample showed smooth wall cavities with no noticeable content, up to 4mm in diameter, which were present below the pleura and also in the depth of the pulmonary parenchyma. Because of this, both lung samples had a sponge-like appearance [Figure 1c]. Tissue samples were routinely processed, embedded into paraffin blocks and classically hematoxylin-eosin stained.

Figure 1. Radiological and macroscopic findings.

Figure 1a. Apical computed tomography of the chest detected numerous diffuse thin-walled cysts of various dimensions without content (arrows)

Figure 1b. Apicoaxial computed tomography of the chest: numerous thin-walled cysts without content (arrows) diffusely presented in the lung parenchyma and subpleurally

Figure 1c. Macroscopic findings: diffuse cystic spaces of the thin and smooth walls, without content. On this sample, the greatest measured diameter is up to 4mm (arrows)

Macroscopic changes were less pronounced on the sample from the right lung, operated one week later.

Suspicion on lymphangioleiomyomatosis arose after H&E staining which has also immunohistochemically proven.

Microscopic finding: In the lung parenchyma were present numerous cystic spaces without content covered by single-row endothelial cells. Under endothelial cells focally have located multiplied spindle cells expressing α -smooth muscle (α SM) actin marker (Figures 2a, b, c). Between these cells are those that express steroid receptors, estrogen and progesterone (Figures 2d, e). The main characteristic is the presence of diffuse cytoplasmic expression of HBM-45 in almost all spindle cells (Figure 2f).

Figure 2. Microscopic findings

Figure 2a. Diffuse changes in the lung parenchyma in the wall of cystic spaces of proliferative spindle cells (arrows) x 10

Figure 2b. One of the focuses of proliferating spindle cells in the wall of the cystic lung structure (arrow) x 20

Figure 2c. α SM actin expression in the proliferative spindle cells that confirms their smooth-muscle origin (arrows) x 10

Figure 2d. Expression of steroid estrogen receptor confirms hormonal dependence of LAM and its most common clinical manifestation during hormonal imbalance (arrows) x 10

Figure 2e. Expression of steroid progesterone receptor in a few tumor cells (arrows) $\times 10$

Figure 2f. HBM-45 expression in spindle cell confirms diagnosis of LAM, (arrows) $\times 20$

A few days after the first, a second intervention of the same type was done in the right lung which had the same changes present but of some lower intensity.

After bilateral surgery, recovery and concurrent pathohistological diagnosis of LAM, our patient should start with the treatment.

DISCUSSION

According to the 2015 WHO Classification of Lung Tumors, LAM belongs to the group of PEComatous tumors, together with benign and malignant PEComatous tumors and “clear cell” tumor. All tumors in this group are characterized by focal or diffuse expression of HBM-45 [1].

The morphological picture of LAM is characterized by the presence of cystic spaces covered by single-row, flat endothelial cells expressing podoplanin (*clone D2-40*) under which are focally located multiplied proliferations of spindle cells expressing α SM-actin. Between these cells are present those expressing steroid receptors, estrogen and progesterone and those with diffuse and cytoplasmic expression of HBM-45. According to some authors, if there is no HBM-45

expression it is about lymphangiomyomatosis. In the first sample in our patient changes are more pronounced than in the other which has also been described in the available literature. Although changes were of varying intensity, both caused pneumothorax [1, 3, 4, 5].

The literature has described cases of LAM that caused pneumothorax in the last trimester of pregnancy and shortly after birth. This phenomenon is explained by the fact that hormonal stimulation during pregnancy leads to an increase in cystic structures and at the end of pregnancy or shortly after delivery it comes to decline in hormonal stimulation and consequently to the rupture of some of the thin wall cystic structures and onset of pneumothorax. This also explains the fact that LAM is almost typically a female disease [3, 5].

LAM can be associated with other diseases but it can be also an independent disease. The Polish authors analyzed 15 pathohistologically diagnosed LAMs and in 6 of them there was no present an associated disease as well as in our patient [5].

After the diagnosis of LAM, the pulmonologist should start treatment with target therapy. Treatment for LAM is based on its etiology. LAM occurs as congenital (TSC-LAM) or acquired (sporadic or S-LAM) tumor suppressor tuberous sclerosis complex (TSC) gene mutation in TSC1 (hamartin) or TSC2 (tuberin). The TSC1–TSC2 complex is incorporated into various signal pathways and it is also involved in the regulation of the target of rapamycin complex. In most LAM tumor tissue, there are either TSC1 or TSC2 mutations, but in 10–15% it is not determined presence of TSC gene mutations. Numerous studies have included the effects of sirolimus which is mechanical target of rapamycin (mTOR) inhibitors. Other molecular - target drugs are also being investigated. If LAM does not respond to these drugs only treatment option is bilateral lung transplantation [6, 7, 8].

CONCLUSION

Lymphangioliomyomatosis is a rare lung tumor manifested by a dramatic clinical picture. In our patient, end of pregnancy caused a decrease in hormones, estrogens and progesterone, which was manifested by lymphangioliomyomatosis in the form of bilateral spontaneous pneumothorax.

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