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Features of Diagnosis and Treatment of Endometriosis-Associated Pneumothorax (Clinical Case)

We describe a clinical case of diagnosis and treatment of a patient of reproductive age with endometriosis-associated pneumothorax. The presented clinical case is quite rare and draws attention to the importance of creating clinical guidelines for the management of patients with endometriosis-associated pneumothorax, since in the described clinical case the diagnosis was not immediately established, which led to complications, and therefore the chosen treatment tactics were not effective enough, which led to relapse. In this case, a protocol for the treatment of patients with bullous emphysema was initially chosen, but in such cases it is necessary to establish other causes of these conditions, in particular, the diagnosis of extragenital endometriosis in order to verify/refute such pathology. As a result of the surgical treatment, the pneumothorax was eliminated, and the quality of life improved, but periodic deterioration and relapses have occurred. Therefore, it indicates the need for an integrated approach to the diagnosis of pneumothorax with the establishment of its etiology, and in case of presence of extragenital endometriosis, the inclusion of a treatment protocol for this disease in the general treatment tactics. The clinical case confirms that in order to choose the most effective type of treatment, a multidisciplinary approach to the diagnosis and treatment of such disease is necessary with the involvement of a wide range of specialists: thoracic surgeons, gynecologists, endocrinologists, pathologists. An important component of an integrated approach to the treatment of such patients is the need for further monitoring of the efficacy of endometriosis treatment, timely diagnosis of its possible spread or complications, as well as monitoring and preservation of the patient's reproductive function.

Keywords

Thoracic endometriosis syndrome, pneumothorax, surgery, hormonal therapy, ultrasound diagnostics.

Endometriosis is defined as the presence of endometrioid tissue outside the uterus [30]. Since the clinical diagnosis requires visualization of endometriosis foci (most commonly by the means of laparoscopy and thoracoscopy) and pathological verification, its prevalence remains unclear, but according to some literature sources, it reaches 10 % among women of reproductive age [30]. According to other data presented by Shafrir et al., this value varies from 2—11 % in women with no complaints to 5—21 % among those hospitalized with pelvic pain [22].

About 12 % of patients with endometriosis have its extragenital forms [17], and the most common localization of these foci apart from the abdominopelvic cavity is the thoracic cavity. The manifestations of endometriosis of this localization are integrated into the thoracic endometriosis syndrome (TES), which includes catamenial pneumothorax (CP), catamenial hemothorax (CHt), catamenial hemoptysis (CH) and pulmonary nodules, as well as some other less common manifestations [17]. Endometrioid structures are located in the pulmonary parenchyma (including bronchi), pleura, and

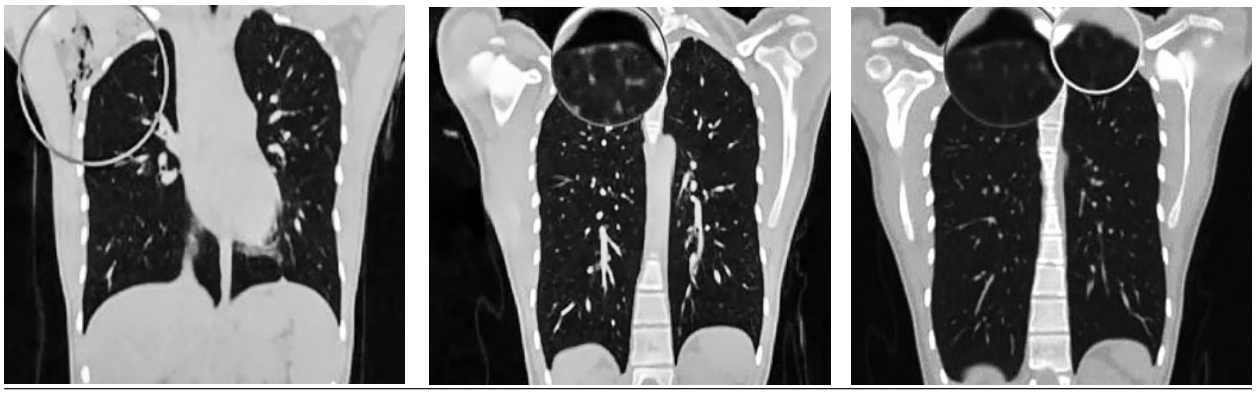

Figure. **Chest CT scan (May 28, 2019)**

diaphragm. Furthermore, it has also been proposed to include catamenial thoracic pain, diaphragmatic hernias, and pleural effusion into the TES [3]. TES is often associated with endometriosis of the urinary, reproductive, and digestive systems. In particular, 50—84 % of patients with TES have concomitant pelvic endometriosis [10].

The most common manifestation of the TES is the CP, accounting for 72—73 % of cases of this pathology [29]. In addition, some authors describe cases of non-catamenial pneumothorax associated with TES (occurring between menstruation periods and in women who no longer have menstruations) [21, 27], so instead of the CP, we will use the term endometriosis-associated pneumothorax (EAP) in this paper. In the structure of pneumothorax among women of reproductive age, the EAP accounts for 7,3 to 36,7 % of cases [6], and the growth of this value from 3—6 % to such numbers in recent years is believed to have been facilitated by a more differentiated approach to the diagnosis of this pathology [27].

Considering the relative rarity of the EAP and the lack of specialized international clinical guidelines for its management, difficulties with timely diagnosis and selection of the optimal treatment of this pathology often occur. In addition, a few cases of the EAP have been described, which can cause difficulties with the differential diagnosis of primary spontaneous pneumothorax and, as a result, delayed or inappropriate treatment [23, 26].

Thus, the objective of our work was to review the clinical case of the EAP, analyze the applied diagnostic and therapeutic tactics, evaluate their efficacy in this clinical case and suggest the diagnostic and therapeutic algorithm for cases of the suspected EAP.

Clinical Case

Patient V., 18 years old, female, on May 24, 2019, was hospitalized to a medical institution with complaints about pain in the right scapula, dry cough, subfebrile temperature and general weakness. Anamnesis of the disease: she became ill acutely 2 days ago. General history (examination of organs and systems): day 4 of the menstrual cycle. The following instrumental examinations were performed: May 24, 2019 — chest radiography: right-sided pneumothorax.

On May 24, 2019, she underwent treatment: thoracoscopy on the right side of the chest, Bühlau drainage of the right pleural cavity (solitary bullae of the right lung were visualized during the surgical intervention).

On the third postoperative day, a follow-up chest radiography was performed. Conclusion: the lungs were decompressed, the sinuses were free and the diaphragm was clear. On the same day, magnetic resonance imaging of the abdominal cavity and pelvic organs (MRI of the abdomen and pelvis) was performed to detect endometrioid foci-no pathological changes detected.

May 28, 2019 — the patient was discharged from the hospital on the 4th day with improvement in her general condition and with a diagnosis: pulmonary bullous emphysema, complicated by right-sided pneumothorax. Recommendations: follow-up by a surgeon at the place of residence, monthly restriction of physical activity, use of analgesics in case of pain, breathing exercises, removal of the drainage suture in 7 days, a routine computed tomography (CT) of the pericardium without intravenous (IV) contrasting (for the differential diagnosis of the disease).

On May 28, 2019, a chest CT scan was performed without IV contrast (Figure).

Chest CT was performed without IV contrast. Description: irregularly shaped hypodense areas are visualized in the subcutaneous adipose tissue of the axillary region (green circle), which are in proximity to denser surrounding tissues. Free air is detected in the pleural cavity in the projection of the apex of the right lung (red circles), with complete collapse of the lung tissue. No signs of tension pneumothorax. No displacement of the mediastinum.

At the level of the lung apices (blue circle), solitary small thin-walled bullae are visualized with no signs of inflammatory changes in the surrounding tissues. No signs of pneumothorax or other complications. Conclusion: condition after drainage of the right pleural cavity regarding pneumothorax. Right-sided apical pneumothorax. Solitary small apical bullae of the left lung. Subcutaneous emphysema.

On April 14, 2020, patient was re-admitted to the hospital with complaints about dry cough, pain in the right scapula, subfebrile temperature. Upon hospitalization, the following tests were performed: complete blood count (CBC), blood biochemistry, urinalysis (UA), and electrocardiography (ECG) — all within normal ranges. A right-sided pneumothorax was diagnosed on the chest X-ray.

Considering the significant collapse of the right lung and the recurrence of pneumothorax on the right, on April 14, 2020, a surgical intervention was performed: right-sided thoracoscopy, Bühlau drainage of the right pleural cavity. The next day, patient underwent a full-scale surgery: video-assisted thoracic surgery without intubation (NIVATS), atypical resection of S1, S3 lung segments, mechanical pleurodesis, Bühlau drainage of the right pleural cavity.

On April 17, 2020, a follow-up chest X-ray was performed. Conclusion: condition after right-sided pneumothorax, atypical resection of S1, S3 lung segments. Right pleural cavity drained, left-sided apical pneumothorax. The next day, repeated follow-up chest X-ray was performed — positive dynamics in the left pleural cavity was observed in comparison to previous examinations. On April 20, 2020, an ultrasound examination of the pleural cavities was performed, during which no fluid in pleural cavities was detected.

On April 21, 2020, the patient was discharged from the hospital on day 6 with the following diagnosis: pulmonary bullous emphysema, right-sided recurrent pneumothorax, left-sided pneumothorax. The patient was provided with recommendations.

On June 02, 2020, patient was re-admitted to the hospital with complaints about worsening of the general status, pain in the left scapula, dry cough, shortness of breath, subfebrile temperature. General anamnesis: day 3 of the menstrual cycle. Upon hospitalization, the following laboratory and instrumental studies were performed: CBC, blood biochemistry, UA — all within normal ranges, ECG — sinus rhythm, bradycardia (heart rate 49 BPM). Left-sided pneumothorax was visualized on the chest X-ray.

Since the patient was diagnosed with a recurrence of left-sided pneumothorax, on June 03, 2020, a surgical intervention was performed: NIVATS on the left, atypical resection of S1 segment, mechanical pleurodesis, Bühlau drainage of the left pleural cavity. During the surgical intervention, the fenestration of the central tendon of the diaphragm was visualized and tissue samples were taken for further pathological examination — fragments of lung tissue (sample A) and a fragment of diaphragm tissue (sample B). Pathohistological conclusion of the above-mentioned specimens: A. The material contains fragments of lung tissue with the presence of alveoli with disrupted walls and the formation of large cavities, which corresponds to emphysema. A large number of capillaries are present in the interalveolar septa; B. The material shows a fragment of soft tissue covered with mesothelium with signs of hyperplasia. There are no signs of endometriosis within the material provided. Diagnosis: A. Pulmonary emphysema, B. Mesothelial hyperplasia. Recommendations: immunohistochemical examination is recommended to verify the diagnosis.

On June 09, 2020, patient was discharged from the hospital with an improvement in her general status on day 8 with a clinical diagnosis: pulmonary bullous emphysema, left-sided recurrent pneumothorax. At discharge, general surgical recommendations were provided. Moreover, considering the detected focus of extragenital endometriosis, a routine consultation with a gynecologist-endocrinologist was recommended.

July 22, 2020 — immunohistochemical examination (day 9 of the menstrual cycle). Conclusion: moderate positive cytoplasmic expression of CD10, reduced quantity of estrogen receptors.

On August 27, 2020, patient consulted a gynecologist-endocrinologist. The patient complained about profuse and painful menstruation. The duration of menstrual cycles is 29—30 days, the duration of menstruation is 5 days on average. Upon the specialist's recommendation, the following laboratory and instrumental studies were performed: vitamin D (25-hydroxycalciferol) levels — 104 nmol/L, progesterone (day 17 of the menstrual cycle) — 1,85 ng/mL, estradiol (day 5 of the menstrual cycle) — 33 pg/mL, transabdominal pelvic ultrasound — uterus, right and left ovaries — all within normal ranges. Conclusion: ultrasound signs of menstruation. Recommendations: follow-up pelvic ultrasound in 6 months, dydrogesterone 10 mg, 1 tablet once a day from the 5th to the 25th day of the menstrual cycle during the next 5 menstrual cycles.

On April 18, 2023, patient re-visited a gynecologist-endocrinologist with complaints about irregular menstrual cycles, profuse and painful menstruation, and the presence of bloody discharge after menstruation. A gynecological examination and transvaginal pelvic ultrasound were performed: the uterus was intact, the right ovary had follicles of 4—7 mm in diameter and foci of endometriosis up

to 11 mm in diameter, the left ovary was intact. Conclusion: ultrasound signs of the first phase of the menstrual cycle and focal endometriosis in the right ovary. Diagnosis: genital focal (focus in the right ovary) endometriosis and extragenital focal (focus in the lungs) endometriosis. It was recommended to proceed with the prescribed therapy and to undergo a follow-up pelvic ultrasound in 6 months.

October 10, 2023 — patient re-visited the gynecologist-endocrinologist with the same complaints. A gynecological examination and transvaginal pelvic ultrasound were performed: the uterus was intact, right ovary — antral follicles up to 8 mm in diameter, inclusions with «frosted glass» type of content of 13 mm in diameter, left ovary was intact. Conclusion: ultrasound signs of focal endometriosis of the right ovary and the second phase of the menstrual cycle. Clinical diagnosis: genital focal (focus in the right ovary) and extragenital focal (focus in the lungs) endometriosis. Recommendations: dienogest 2 mg, 1 tablet once a day for 6 months, a routine breast ultrasound on days 4—10 of the menstrual cycle, thyroid ultrasound.

The patient continues treatment under the guidance of a gynecologist in compliance with all recommendations. To date, no new episodes of deterioration have been reported.

Discussion

There are several theories regarding etiology and pathogenesis of the TES [17]. According to the theory of retrograde menstruation, endometrial cells move retrogradely through the fallopian tubes into the abdominal cavity, where they can implant into the peritoneum. Once in the right subdiaphragmatic area (they do not stay in the left one due to the specificity of peritoneal fluid circulation), cells implant in the diaphragm and undergo transperitoneal-transdiaphragmatic migration into the pleural cavity through the congenital or acquired fenestrae of the diaphragm. Based on the theory of cellular metaplasia, endometriosis occurs as a result of metaplasia of pleural and peritoneal mesothelium into stroma and glands of the endometrium, in particular, under the influence of estrogen [11, 17]. Lymphatic and hematogenous dissemination of endometrial cells may also occur, usually to lung parenchyma and bronchi.

The pathogenesis of the EAP is also not fully understood, so there are several theories regarding it [20]. These include spontaneous rupture of subpleural blebs, peeling of endometrial inclusions from the visceral pleura with subsequent air leak from the lungs, and air passage into the pleural cavity from the genital tract through congenital or acquired (including those formed due to the peeling of endometrial inclusions) diaphragmatic fenestrae. Prostaglandin F2α, plasma concentration of which is elevated during menstruation, is a powerful bronchoconstrictor and vasoconstrictor, and therefore can cause rupture of the alveoli of preformed subpleural blebs and bullae provoking clinical signs of the EAP [17, 20].

The manifestations and nature of the localization of endometrial foci in the pleural cavity of this patient suggest a combination of several mechanisms of pathogenesis of the TES and the EAP in our case.

The average age of women at the time of onset of symptoms of the TES is (35.0 ± 0.6) years, with a range from 15 to 54 years, while the highest prevalence of pelvic endometriosis is observed at the age of 24—29 years [2]. The age of this patient at the time of onset of the EAP was 18 years, which is not typical.

The EAP manifestations usually occur between 24 hours before and 72 hours after the onset of menstruation [26], but some authors also report about onset of the EAP symptoms 72 hours prior to menstruation [16] and even up to 7 days after the beginning of menstruation [15]. In case of our patient, symptoms occurred generally on days 3—4 of the menstrual cycle.

The vast majority of the EAP cases are localized in the right side of the chest, which is explained by the features of the pathogenesis described above [28], and this trait of the EAP is traced in our clinical case.

Symptoms of the EAP include cough, chest pain, and shortness of breath. About 25 % of women with the EAP have a history of chest or scapular pain during menstruation, and about half have a history of obstetric and gynecological interventions [26]. Thus, the manifestations of the EAP in this patient were quite typical.

In our clinical case, there is also an association of extragenital and pelvic (right ovarian endometriosis) endometriosis, which occurs in about half of the TES cases [10].

Despite their low specificity, the most sensitive diagnostic procedures for visualizing pneumothorax are chest X-ray and chest CT, while MRI is more sensitive for detecting foci of thoracic endometriosis [17]. Mediastinal displacement, pneumomediastinum, pneumoperitoneum, «frosted glass» type of inclusions, bronchial wall thickening, bullae and thin-walled cavities in lung parenchyma, and areas of subcutaneous emphysema can be visualized [12]. Chest X-ray can also be used for differential diagnosis with other diseases (e. g., pleuritis). Either way, chest CT is able to detect diaphragmatic endometrial implants, as well as identify single or multiple pulmonary nodules [17]. In case of our patient, the chest CT revealed the presence of bullous pulmonary emphysema and other signs of spontaneous

pneumothorax, i. e. it provided important information for differential diagnosis.

Bronchoscopy and cytology also play a role in the diagnosis of the TES, but only in cases of bronchopulmonary forms, which are quite rare to occur [5].

Videothoracoscopy as the gold standard for the diagnosis of the TES allows detecting diaphragmatic fenestrations (in case of this patient, during surgery, the fenestration of the central tendon of the diaphragm was visualized), endometriosis of the visceral pleura, bullae, blebs, scars, and perform biopsy (in our case, lung tissue fragments and a fragment of diaphragmatic tissue were taken) for further pathohistological examination [19]. In the absence of contraindications, NIVATS is preferred because of a shorter rehabilitation period, reduced pain, and improved quality of life in patients compared to those who underwent surgical treatment in the form of lateral thoracotomy and VATS [18].

It is important to use immunohistochemical examination of implants for further verification of endometriosis [9, 21, 25]. In case of this patient, this study allowed us to confirm the presence of an extragenital form of endometriosis. In case of suspected endometriosis, it may be useful to use pelvic ultrasound, which allows detecting genital forms of endometriosis [30]. In our case, the data of pelvic ultrasound was one of the most crucial for verifying the diagnosis, since the study revealed focal endometriosis of the right ovary.

The EAP with moderate symptoms is usually treated with simple bed rest and thoracentesis or pleural drainage to relieve symptoms [6]. Hormonal therapy is used in the form of combined oral contraceptives (COCs), progestins, or gonadotropin-releasing hormone (GnRH) agonists and antagonists [24].

Most surgical interventions are performed using thoracoscopy, and pleurodesis is recommended to reduce recurrence rates. Blebectomy or apical sphenoidal pleurectomy is also performed, as well as different types of diaphragmatic interventions, diaphragm suturing and resection. The rarest types of surgical interventions include non-defined wedge resection and middle lobe resection. Surgical intervention for the EAP is usually performed when conservative treatment fails or in case of multiple recurrences of pneumothorax [6, 8, 16]. Recurrence rates can be as high as 30 % when surgery alone is implemented [13]. Since conservative treatment in this case was not performed at the onset of the disease, multiple recurrences of pneumothorax were considered as an indication for surgical intervention. In our case, Bühlau drainage of the pleural cavity was performed, and in cases of recurrence — NIVATS with mechanical pleurodesis was used.

The combined surgical and therapeutic tactics for the treatment of EAP proved to be effective, since after performing the necessary surgical interventions and further implementation of the recommendations of the gynecologist-endocrinologist, the patient has not had any episodes of deterioration for more than a year. The effectiveness of this technique is also confirmed in numerous articles [1, 2, 4, 6—8, 14, 16, 17, 19, 24, 27, 28].

Conclusions

The following patients with spontaneous pneumothorax aged (35.0 ± 0.6) years with a range of 15—54 years should be given special attention based on the case report and literature review.

Onset of clinical symptoms of the EAP mainly correlates with the beginning of the menstrual cycle, although it can occur 3 days before and 7 days after menstruation.

Diagnosis of EAP requires a comprehensive collection of the patient's medical history, including gynecological history, followed by a mandatory consultation with a gynecologist and additional examination to the required extent (transvaginal pelvic ultrasound) to establish or refute the presence of endometriosis.

During videothoracoscopic interventions, it is necessary to conduct a thorough examination of the pleural cavity for possible foci of extragenital endometriosis, and, if present, perform their pathological examination, if necessary — also the immunohistochemical examination.

The combination of surgical techniques (NIVATS and pleurodesis) with hormonal therapy proved to be effective.

Assessment of diagnostic and therapeutic tactics for spontaneous pneumothorax in women should take into account patient's age, gynecological history at the time of hospitalization and should include further comprehensive multidisciplinary approach to confirm or refute the presence of endometriosis as a cause of pneumothorax, and to select the combined surgical and therapeutic treatment strategy.

It is important to initiate the development of clinical guidelines for the diagnosis and treatment of the EAP caused by extragenital endometriosis for the appropriate management of such patients, which will improve treatment outcomes and reduce the cost of diagnostic and treatment procedures.

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Особливості діагностики та лікування ендометріоз-асоційованого пневмотораксу (клінічний випадок)

Нами описаний клінічний випадок проведених діагностики та лікування пацієнтки репродуктивного віку з ендометріоз-асоційованим пневмотораксом. Презентований клінічний випадок є досить рідкісним та звертає увагу на необхідність створення алгоритму ведення пацієнтів з ендометріоз-асоційованим пневмотораксом, оскільки в описаному клінічному випадку не одразу був встановлений діагноз, через який виникли ускладнення, а тому обрана тактика лікування не була достатньо ефективною, що призвело до рецидиву. В цьому випадку на початку було обрано протокол лікування пацієнтів, які мають бульозну емфізему легень, проте в таких випадках необхідним є встановлення інших причин цих станів, зокрема діагностика екстрагенітальної форми ендометріозу з метою верифікації/спростування такого діагнозу. Внаслідок проведеного оперативного лікування було ліквідовано пневмоторакс, спостерігалося покращення якості життя, проте періодичні погіршення стану та рецидиви вказують на необхідність комплексного підходу до діагностики пневмотораксу зі встановленням причини його виникнення та, за умови встановлення наявності екстрагенітального ендометріозу, включення протоколу лікування цього захворювання до загальної тактики лікування. Клінічний випадок підтверджує, що з метою вибору найбільш ефективного виду лікування необхідним є мультидисциплінарний підхід у діагностиці та лікуванні таких захворювань із залученням широкого кола спеціалістів: торакальних хірургів, гінекологів, ендокринологів, патоморфологів. Важливим компонентом комплексного підходу до лікування таких пацієнтів є необхідність подальшого контролю ефективності лікування ендометріозу, вчасна діагностика його можливого поширення чи виникнення ускладнень, а також контроль та збереження репродуктивної функції пацієнтки.

Ключові слова: синдром торакального ендометріозу, пневмоторакс, хірургія, гормональна терапія, ультразвукова діагностика.

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