

This is an analysis of the case of a 46-year-old woman suffering from ovarian metastases of small cell lung cancer. The main symptoms were abdominal pain, vaginal bleeding and weight loss. The ovarian tumor was detected during computed tomography (CT) of the abdominal cavity. X-rays and CT of the chest revealed enlarged mediastinal lymph nodes and a tumor in the right lung. As a result of constant bleeding from the genital tract a total hysterectomy was performed. A histopathological examination of the ovarian tumor confirmed the presence of small cell cancer, most likely as a lung metastasis. Head CT revealed a metastasis in the left parietal lobe. Subsequently, on the basis of the results of immunohistochemical examinations, small cell lung cancer was explicitly confirmed. The patient received four chemotherapy cycles with cisplatin, etoposide and palliative radiotherapy for the lung and brain cancer. Both partial remission and improved clinical status were obtained. Three months later the disease progressed (lung tumor enlargement and numerous brain metastases) and the general condition of the patient deteriorated. Second line chemotherapy was applied at this time. The patient received four cycles with topotecan according to the scheme. The chemotherapy gave unsatisfactory results and was therefore stopped in favor of palliative treatment.

Key words: small cell lung cancer, ovarian metastases, diagnosis, treatment.

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Ovarian metastases as a first symptom of small cell lung cancer

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Introduction

The number of cases of small cell lung cancer has decreased over the years but the percentage of women suffering from this kind of cancer has risen due to an increasing number of female cigarette smokers. At the time of diagnosis of small cell lung cancer 60–70% of the patients are in the disseminated stage of the disease, often with distant metastases. The remaining patients are in the limited stage [1].

The appearance of remote metastases in cases of lung cancer is associated with an unfavorable prognosis. Metastases are most often located in the: bones (25%), central nervous system (20%), heart and pericardium (20%), pleura (8–15%), adrenal gland (2–22%) and liver (1–35%). Kidney, alimentary canal and pituitary gland metastases of lung cancer are diagnosed much less frequently during the patient's life, though in some cases they are identified during autopsy [2]. Ovarian metastases constitute 5–10% of all malignant tumors of this organ whereas ovarian metastases of small cell lung cancer are diagnosed only occasionally [1, 3].

Ovarian cancer symptoms depend on the stage of the disease. They can be restricted to the abdominal cavity or, in the case of metastasis, they may concern involved remote organs [4]. In the diagnostic process the crucial factor is the result of the histopathological examination. Therapeutic procedures include surgical treatment, chemotherapy and radiotherapy [5].

Case description

A 46-year-old patient was admitted to the Pulmonology Unit of the provincial hospital because of weight loss over a 6 month period (about 10 kilograms), effort dyspnea, cough with expectorant mucous secretion, pain in the lower abdomen and genital tract bleeding with variable intensity. The patient had not been sick previously and had smoked 30 cigarettes a day for the past 20 years. Blood tests revealed anemia 6.13 mmol/l, a value for C-reactive protein of 84.44 mg/l and a sedimentation rate of 90 mm after 1 hour.

Chest X-rays revealed a tumor related broadening of the upper right mediastinum and the right hilus. No focal lesion in the lung parenchyma was identified.

Bronchofiberoscopy revealed infiltration of the main carina and the main right and intermediate bronchus, from which a biopsy was taken, and which totally obstructed the bronchus up to the upper right lobe.

Ultrasonography of the abdominal cavity, in association with a gynecological examination, revealed a homogeneous lesion in the left adrenal gland 5.7 cm × 3.9 cm, having the characteristics of tumor metastasis. In the lesser pelvis a homogenous 15.0 cm × 10.0 cm tumor was identified, which



Fig. 1. Lymph node mass in the mediastinum, tumor infiltration leading to intermediate bronchus stenosis and closure of the bronchus up to the lower lobe, lower lobe atelectasis, infiltrations in other parts of the parenchyma and liquid in the pleural cavity, pressure and probable infiltration of the left atrium and the superior vena cava.

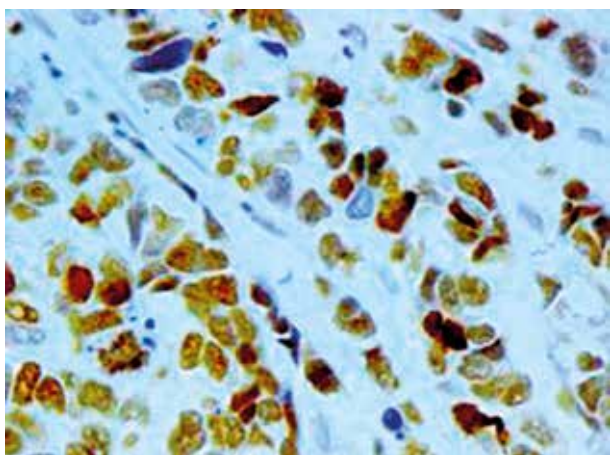


Fig. 2. Ovarian tumor. The nuclei of cancer cells are positive for TTF-1 (magnification 40×)

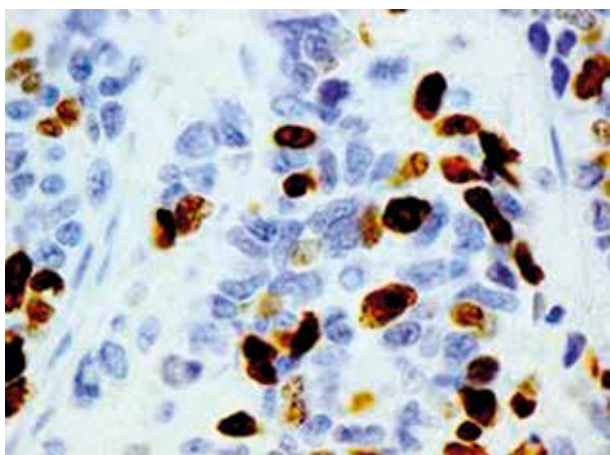


Fig. 3. Reactivity of ovarian tumor cells for Ki67 (magnification 40×)

started from the ovary (it was difficult to identify the side), and enlarged lymph nodes up to about 2.9 cm around the aorta.

Computed tomography revealed a 12.5 cm × 10.5 cm polycystic mass in the right ovary. The tumor comprised liquid filled spaces of up to 7.0 cm diameter. A homogeneous isoechogenic lesion in the right adrenal gland was also identified. In the retroperitoneal space, and in the spleen cavity, enlarged lymph nodes were identified of 6.0 and 6.5 cm total dimension. Remnants of liquid in the Morrison recess were identified.

Diagnostic imaging was complemented with computed tomography of the chest. The following were identified: a lymph node mass in the mediastinum, tumor infiltration leading to intermediate bronchus stenosis and closure of the bronchus up to the lower lobe (lower lobe atelectasis), infiltrations in the other parts of the parenchyma and liquid in the right pleural cavity. There was also pressure on, and probably infiltration of, the left atrium and the superior vena cava. The maximum size of the pathological mass was 8.0 cm × 11.0 cm. Additionally, a left adrenal gland metastasis was identified (Fig. 1).

On the basis of the tests performed, a disseminated tumor process was diagnosed with an indeterminate primary site. The ovary was assumed to be the most probable location for the primary tumor, with the lung being the second most probable location. Small cell cancer was identified. Histopathological examination of the bronchial biopsy revealed thick tumor infiltration comprising small cells with scant cytoplasm. Immunohistochemical tests against CK AE1/3+/- ("dot-cell" type reaction), Ki 67, NSE and chromogranin were carried out, though the results were unreliable. The histopathological picture led to suspicion of anaplastic small cell cancer. To complete the diagnosis, additional immunohistochemical tests (LCA and TTF1) were performed.

Before the final histopathological report was obtained, the patient underwent a surgical procedure due to the constant genital tract bleeding. A modified radical hysterectomy and bilateral salpingo-oophorectomy were performed. Macroscopically, in the right ovary, there was a 6.5 cm × 5.5 cm × 5.3 cm encapsulated tumor with necrosis. In the left ovary a necrotic tumor measuring 12.5 cm × 10.0 cm × 7.0 cm was identified, with a focally ruptured cyst. On the basis of the immunohistochemical examination, the histopathology report confirmed the diagnosis of small cell anaplastic cancer, probably arising from a lung cancer metastasis (Figs. 2–6). Shortly afterwards, the final confirmation of small cell lung cancer was obtained from the bronchial biopsy which showed positive immunohistochemical reactions for TTF-1, Ki67, CK-7 and chromogranin (Figs. 7–8).

The patient was transferred to the Pulmonology, Allergology and Respiratory Oncology Clinic in Poznan with the aim of continuing the treatment. On admission, suppressed percussion sounds were noted as well as feebleness of the vesicular murmur over the right lower lung area and superior vena cava indicators. Chest radiograms and ultrasonography revealed the presence of liquid in the right pleural cavity up to the angle of the scapula. Thora-

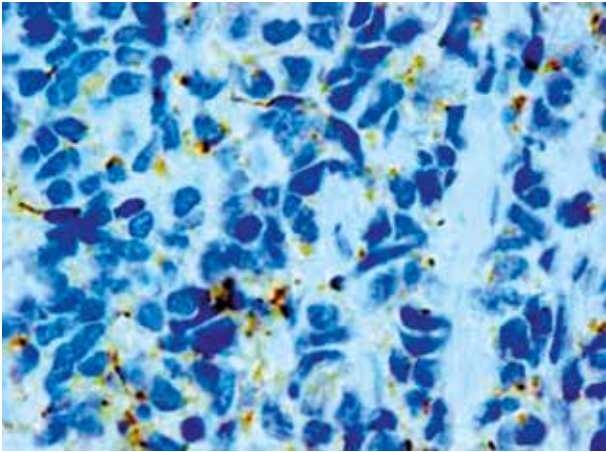


Fig. 4. Ovarian tumor cell cytoplasm is positive for chromogranin (magnification 40×)

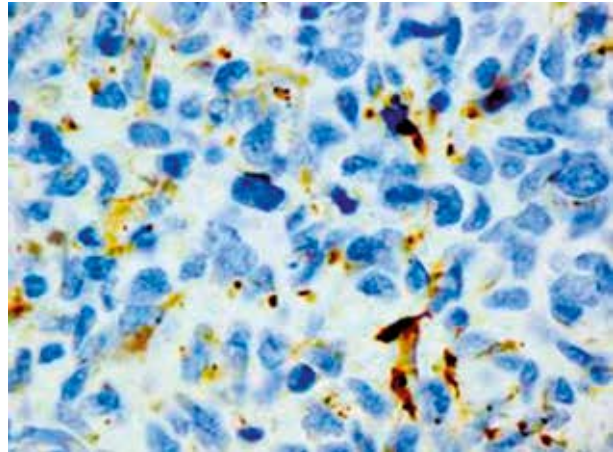


Fig. 5. Ovarian tumor. Immunohistochemistry for CK7 (40×)

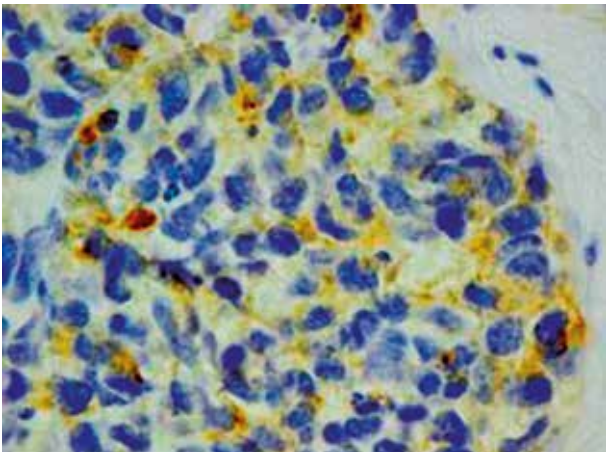


Fig. 6. Ovarian tumor. Immunohistochemistry for synaptophysin (magnification 40×)

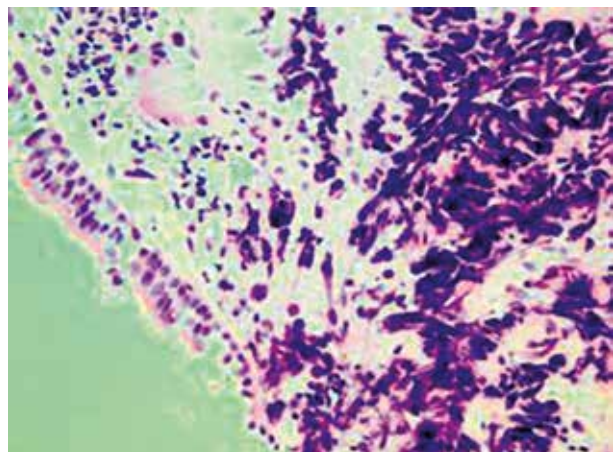


Fig. 7. Bronchial biopsy. HE, (magnification 20×)

centesis was performed twice, resulting in the discharge of a total of 2600 ml of bloody liquid. The diagnostics were completed with tomography of the head which revealed a lesion of 1.0 cm diameter in the left parietal lobe with morphological characteristics suggestive of metastasis (Fig. 9).

The treatment comprised four chemotherapy cycles, according to the PE scheme (etoposide, cisplatinum), radiotherapy to the right lung-mediastinal area (8 Gy) and radiotherapy to the brain (6 Gy). Clinical improvement was obtained, superior vena cava syndrome symptoms subsided, total brain tumor and partial lung tumor remission was observed and the pleural exudate diminished. After a 3-month recovery period, disease progressive was reported. The lung tumor became enlarged and the volume of exudate increased (Fig. 10). In second line treatment, four topotecan cycles were applied according to the scheme, which led to stable disease. Another progression took place after a period of less than 4 months. Partial, right side limb paresis was observed, as well as speech impediments, dizziness and headaches. Computed tomography of the head revealed the occurrence of numerous brain metastases. Fig 11. The patient underwent palliative brain radiotherapy (6 Gy) resulting in a reduction of the neurological disorders.

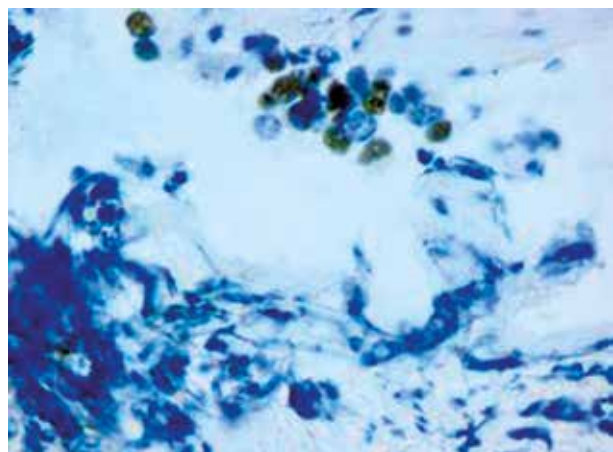


Fig. 8. Bronchial biopsy . Immunohistochemistry for TTF-1 (magnification 40×)

The patient was discharged from the Clinic with the recommendation to continue the treatment in her local Palliative Care Clinic.

Discussion

The patient in the described case was diagnosed with small cell lung cancer with coexistence ovarian metastases.



Fig. 9. Metastasis of small cell lung cancer in the left parietal lobe



Fig. 11. Metastasis of small cell lung cancer to both cerebral hemispheres

ses. In this case abdominal pains, genital tract bleeding and significant weight loss were the main symptoms and preceded the disorders of the respiratory system and the final diagnosis of small cell lung cancer. The identification of ovarian metastases is not difficult in the case of previously identified lung cancer.

Irving and Young stated that the incidence of identification of a primary lung tumor, prior to the identification of an ovarian metastasis was 53% in a 12-month period. In 31% of cases lung cancer and metastases were diagnosed simultaneously and, in case of 16% of patients, the identification of ovarian metastases preceded the identification of lung cancer by 2–26 months. 44% of ovarian tumors were identified as small cell cancer, 34% as adenoma and 16% as large cell carcinoma. There was one case of squa-

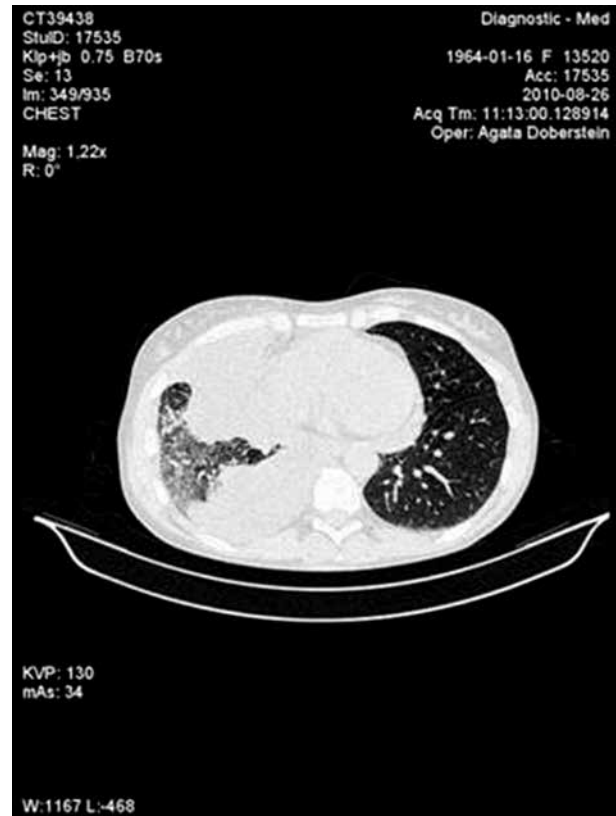


Fig. 10. Lymph node mass in the mediastinum. Tumor infiltration in the right lung and liquid in the pleural cavity

mous cell carcinoma and one carcinoid. The largest ovarian tumor was 22.0 cm, the smallest 1.0 cm, giving an average of 9.7 cm. In the cases of one third of the patients, the metastases concerned both ovaries. Cancer was limited to the lung and one or both ovaries in the cases of 40% of the patients. In the remaining 60% of cases, coexistence of the following metastases were identified: brain, uterus, peritoneum, bones, breast, liver, colon, lymph glands, mediastinum and pelvis as well as the pericardium, chest wall, spleen, salivary glands and parathyroid glands.

It has been shown that smoking increases the risk of lung cancer and ovarian metastases. In the case of small cell ovarian cancer, 28% of the patients are smokers [1].

In the presented case small cell lung cancer metastases were identified in both ovaries, in the left adrenal gland and the brain. Macroscopically, ovarian tumors were encapsulated, necrotic and relatively large: 6.5 cm and 12.5 cm. The diagnosis of small cell ovarian cancer as a metastasis of small cell lung cancer was based on diagnostic imaging, macroscopic evaluation and the results of immunohistochemical tests on biopsied tissue from the lung and ovaries.

The morphological characteristics of metastases are common for many ovarian tumors and can appear with multitumor hyperplasia, extensive necrosis, blood and lymph vessel infiltration, or with infiltration of the surface of the ovary [5].

Crowder and Tuller determined that the incidence of small cell cancer constitutes less than 2% of all malignant tumors of the genital organs among women. Most often

the disease process involves the cervix, though it may also be present in the ovary, endometrium, vagina, fallopian tubes or vulva. Two types of primary ovarian small cell cancers are recognized: a pulmonary type and a hypercalcemic type. The first is microscopically indistinct from lung cancer. The tumors are of highly malignant character. They have tendency to infiltrate surrounding structures and to create remote metastases. In the cases of a few patients, the disease process may be symptomless. Most of the patients complain of stomachaches and flatulence as well as recurring genital tract bleeding. Eichhorn and co. precisely described this subtype of the primary ovarian tumor, which is microscopically indistinct from metastatic small cell lung cancer. This is an undifferentiated carcinoma which develops in females aged between 28 and 89 years of age (average age 59 years). The tumor is highly malignant, as is small cell lung cancer, and is often bilateral [6–8]. The focal presence of a surface epithelial tumor (eg endometrioid type) or the coexistence of lesions such as Brenner tumors are sometimes helpful in excluding metastasis. In the absence of such a finding and in the presence of tumor in the lung, it may be impossible to decide whether an ovarian small cell carcinoma of pulmonary type is primary or metastatic [9].

The hypercalcemic type of small cell ovarian cancer develops in younger women (average 46 years). A case of ectopic Cushing syndrome was identified in one case of a patient suffering from small cell vaginal cancer, hypercalcaemia and incorrect secretion of antidiuretic hormone [4]. The histological structure of hypercalcemic type cancer is characteristic and differs from the pulmonary type. In addition, hypercalcemic type cancers are negative for TTF1.

In the treatment of ovarian metastases of small cell lung cancer, surgical removal of the involved ovaries and, in some cases, total hysterectomy are carried out. Chemotherapy (4–6 cycles) according to the EP scheme (etoposide, cisplatinum), is established for small cell lung cancer. There is an alternative procedure comprising of a triple therapy; cyclophosphamide, doxorubicin and vincristine or etoposide, though this method is usually less efficient and more toxic. Patients with small cell lung cancer regression have an unfavorable prognosis, with an average of survival time of 3–4 months, which however depends on tumor localization and size. Second line monotherapy comprises pharmaceuticals such as topotecan, carboplatin, irinotecan, vinorelbine, paclitaxel or docetaxel. Topotecan is the most commonly used pharmaceutical with a response to treatment of 25–35% and a survival time of 3 months. The treatment may also use a combination of two or three medicines according to the EP scheme and CAV (cyclophosphamide, doxorubicin, etoposide) [10–12].

In the case described above, the procedure was consistent with the established rules and included total hysterectomy, first- and second-line chemotherapy, palliative brain and right lung-mediastinum area radiotherapy.

In conclusion, in cases where ovarian small cell cancer is diagnosed, the coexistence of a primary small cell lung cancer is highly probable. The presence of disturbing symptoms in the genital tract area in women with diagnosed lung cancer should raise suspicions of metastasis.

In differential diagnostics it is important to take into consideration primary ovarian tumors and other metastases to other organs [4].

The authors declare no conflict of interest.

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