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Exophthalmos as a first manifestation of the systemic spread of small cell lung cancer

Wytrzeszcz gałki ocznej jako pierwszy objaw rozsianej postaci raka drobnokomórkowego płuc

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Streszczenie: Small cell lung cancer is characterized by rapid growth and early metastases. The most frequent locations of the secondary lesions include adrenal glands, brain, liver, and skeleton. On initial diagnosis, up to 70% of patients with small cell lung cancer have metastases. Metastases to the eye or orbit developen approximately 0.7–12% of patients with lung cancer. Clinical signs and symptoms of orbital metastases may include exophthalmos, diplopia, pain, limited ocular motility, blurred vision, swollen eyelid, conjunctival hyperemia and edema, increased ocular pressure and papilledema. Here, we report a rare case of exophthalmos as the first manifestation of a metastatic tumor of orbit due to small cell lung cancer.

Słowa kluczowe: exophthalmos, lung cancer, orbital metastases.

Summary: Rak drobnokomórkowy płuc charakteryzuje się szybkim wzrostem i wczesnym tworzeniem przerzutów. Zmiany wtórne najczęściej umiejscawiają się w: nadnerczach, mózgu, wątrobie oraz w układzie kostnym. Już podczas wstępnego rozpoznania raka drobnokomórkowego płuc przerzuty ma nawet 70% pacjentów. Zmiany przerzutowe do oczodołu i gałki ocznej rozwijają się u około 0,7–12% chorych. Przerzuty do oczodołu mogą manifestować się takimi objawami klinicznymi jak: wytrzeszcz, dwojenie, ból oka, ograniczenie ruchomości gałki ocznej, zamglone widzenie, obrzęk powiek, przekrwienie i obrzęk spojówki, wzrost ciśnienia wewnątrzgałkowego oraz obrzęk tarczy nerwu wzrokowego. Przedstawiamy rzadki przypadek wytrzeszczu gałki ocznej, który jest pierwszym objawem zmiany przerzutowej raka drobnokomórkowego płuc do oczodołu.

Key words: wytrzeszcz gałki ocznej, rak płuc, przerzuty do oczodołu.

Lung cancer is one of the most prevalent human malignancies; approximately 1.3 million of patients die due to this tumor yeach year. It is the most frequent oncological cause of mortality among men, and the second cause of oncological deaths in women, surpassed only by breast cancer. Clinically, two types of primary pulmonary malignancies are distinguished: small cell lung carcinoma and non-small cell lung carcinoma, which include planoepithelial cancer, large-cell cancer, and adenocarcinoma. Among pulmonary neoplasms, small cell lung cancer (SCLC) shows the highest aggressiveness. It is characterized by rapid growth and strong predisposition to early formation of metastatic lesions (1). The most frequent locations of the secondary lesions include adrenal glands, brain, liver, and skeleton. On initial diagnosis, up to 70% of patients with SCLC present with metastases.

Usually, the clinical symptoms associated with the location of primary and secondary lesions can be observed in diagnosis of disseminated SCLC. These are the symptoms which prompt the patient to come and see physician. The cases of asymptomatic disseminated malignancy are extremely rare, and the situations in which it is the ophthalmologist who establishes the correct diagnosis should be considered unique. We present such an exceptional clinical case, illustrating a relatively unusual course of primary disseminated pulmonary malignancy, with exophthalmos as the first and only clinical symptom.

Case report

A 72 year-old farmer referred to the Department of Ophthalmology in Bialystok due to exophthalmos of the left eye progressing for a period of one month. The symptoms exacerbated two weeks earlier, when exophthalmos was accompanied by eye pain and deterioration in vision. Twelve years earlier the patient was operated due to the cataract of the right eye with extracapsular method, manual removal of nucleus, and the implantation of artificial posterior chamber intraocular lens (PC-IOL). Several years later he experienced luxation of PC-IOL into the vitreous body along with the retinal detachment associated with the injury of previously operated eye. The patient refused proposed surgical treatment (pars plana vitrectomy with secondary implantation of posterior chamber lens with scleral fixation). He had no family history of ophthalmological conditions.

Patient's overall status included one-year long history of arterial hypertension, ischemic heart disease, and hypercholesterolemia treatment. He experienced a myocardial infarction, which was treated with percutaneous coronary intervention, in 2007. The patient admitted to quitting smoking 10 years earlier, prior to that he smoked for more than 40 years, approximately one package per day. On admission, the patient had no general complaints and took the following medications:

Polocard, Bisocard, Rawel SR, Ranopril, and Simvasterol. He had no family history of cancer.

The general status of the patient was good on admission. He weighed 70 kg for 167 cm of body height, and no abnormalities were documented on the subjective global assessment (SGA) of nutrition. An initial ophthalmological examination revealed exophthalmos of the left eye; the examination with Hertel exophthalmometer revealed the following asymmetry of eye alignment: 15 mm in the right eye (RE), and 23 mm in the left eye (LE). The exophthalmos was not reduced by eye compression; neither pulsation nor hums on orbital auscultation were documented. Furthermore, the left eye was slightly externally repositioned. Its mobility was limited in all directions, with most pronounced limitation in temporal-superior direction. The mobility of the right eye was normal. Bone edges of both orbits were smooth and painless on palpation. On admission, the visual acuity was 0.5/50 in RE, and 5/16 in LE, Sn for near vision in LE was 1.25 cc +3.75 Dsph. Color perception was normal in both eyes and the intraocular pressure in RE and LE was equal to 12 mmHg and 15 mmHg, respectively. Aside from slight irritation of left conjunctiva, the anterior segments of both eyes were normal. The post-surgical lack of the lens was confirmed in the right eye, with the injury of the posterior capsule, and the posterior chamber implant fixed in the vitreous body, with a fragment of upper haptene visible in the pupil. Opacity of lens nucleus was observed in LE. Fundus examination of the right eye revealed pale pink and flat optic disc with distinct borders. The retinal vessels were constricted, inferior flat detachment of the retina involving the macula was noted. Hyperemic optic disc with elevated, effaced borders was detected on fundus examination of the LE. The retinal arteries were constricted, while the retinal veins were dilated and curly. Solitary drusen were present in the posterior pole (Fig. 1).

Fig. 1. Fundus of the left eye: hyperemic, elevated optic disc with effaced borders. Venous vessels dilated and curly.
Ryc. 1. Dno oka lewego – tarcza nerwu wzrokowego przekrwiona, uniesiona, o zatartych granicach. Naczynia żylne poszerzone i kręte.

Ultrasonography of the right eye revealed inferior flat detachment of the retina, whereas a slight elevation in the optic disk projection (swelling of the disc), and a large tumor-like structure in the orbit were detected in the left eye (Fig. 2 and 3).

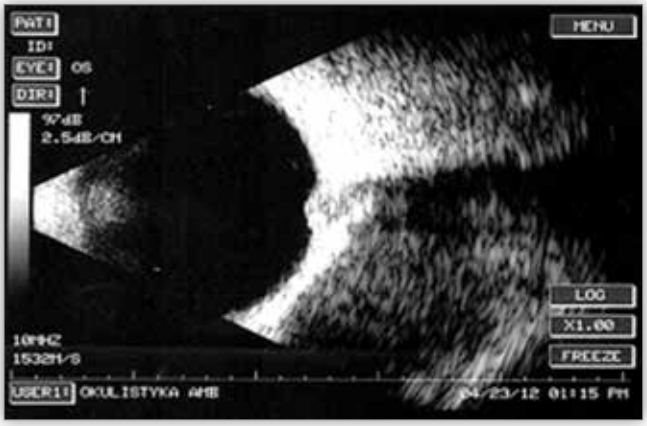

Fig. 2. Swelling of the optic disc of the left eye in B-scan.
Ryc. 2. Obrzęk tarczy nerwu wzrokowego oka lewego w obrazie ultrasonograficznym w prezentacji B.

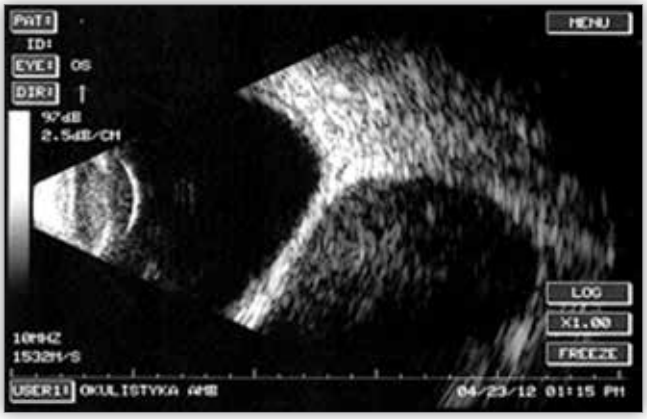

Fig. 3. Tumor of the left orbit in B-scan.
Ryc. 3. Guz oczodołu lewego w obranie ultrasonograficznym w prezentacji B.

Further imaging of the orbit, head, lungs, and abdominal cavity was ordered to find lesions of similar character, potentially corresponding to primary or metastatic foci. However, we did not expect that the tumor found in the orbit will be eventually revealed as "the tip of the iceberg". The results of further tests uncovered a surprising clinical situation. The most important of the abnormalities found in the investigations are listed below in the same order as they were performed.

Computed tomography of the head and orbit with and without contrast agent

A hyperintensive tumor-like structure, approximately 24 x 22 mm in size, poorly enhanced after administration of contrast agent, visible in the left orbit centrally and medially, behind the eye. The lesion compresses ophthalmic nerve (Fig. 4 and 5). Medial rectus muscle was not visualized in the mass of the tumor. Moreover, a small tumor with similar morphology, about 4 x 4 mm in size, detected in the right orbit, next to the medial edge of the medial rectus muscle.

Furthermore, a small hyperintensive focus, approximately 7 x 8 mm in size detected in the right temporal region, next to the wall of Meckel's cavity and sphenoid sinus; it was enhanced after the administration of contrast agent. Hyperintense lesion of similar character, possibly corresponding to a metastasis, visible on the vault of the right parietal region.

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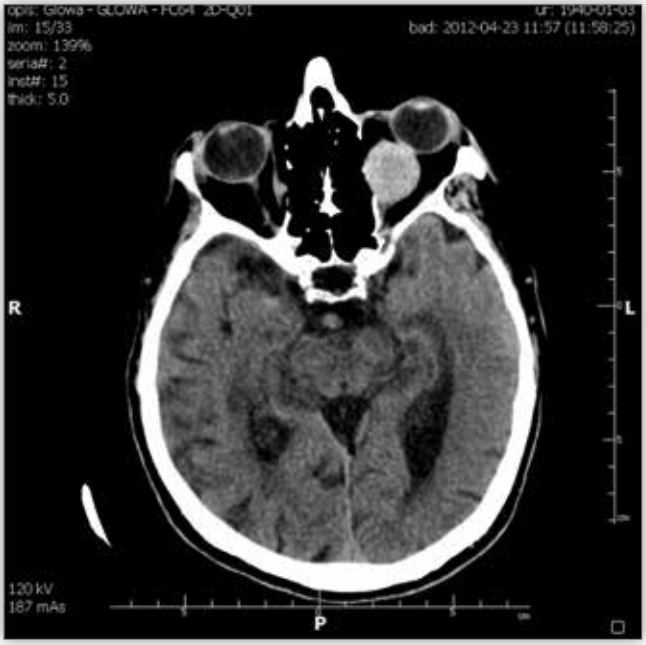

Fig. 4. Large tumor-like lesion behind the left eye and a small lesion next to the medial rectus muscle of the right eye visualized on T1-weighted CT scan in axial cross-section.

Ryc. 4. Duża zmiana guzowata za gałką oczną lewą oraz niewielka zmiana przy mięśniu prostym przyśrodkowym oka prawego – widoczne w obrazie T1-zależnym tomografii komputerowej w przekroju osiowym.

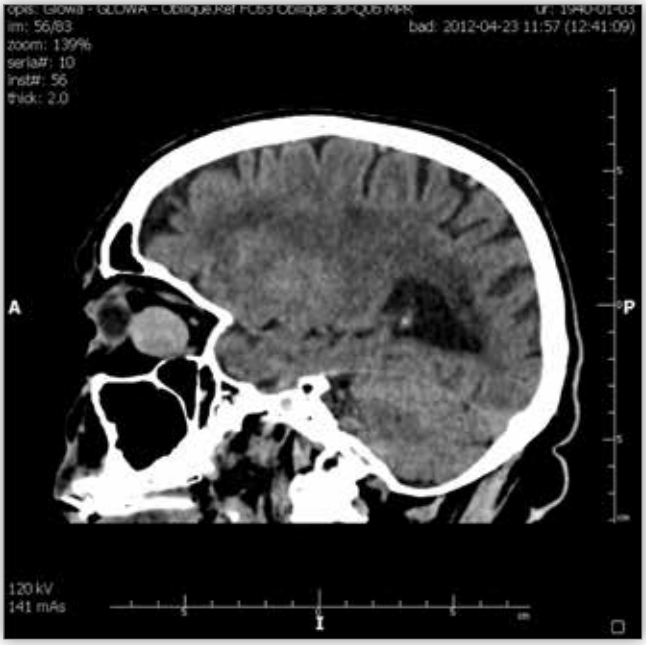

Fig. 5. Large tumor-like lesion behind the left eye visualized on T1-weighted CT scan in sagittal cross-section.

Ryc. 5. Duża zmiana guzowata za gałką oczną lewą widoczna w obrazie T1-zależnym tomografii komputerowej w przekroju strzałkowym.

Magnetic resonance imaging of the head and orbit, with and without contrast agent

A retrobulbar, extraconal tumor-like structure, approximately 23 x 21 x 24 mm in size (LR x HF x AP), was detected in the medial part of the left orbit, without evident enhancement following the administration of contrast agent. The lesion is well

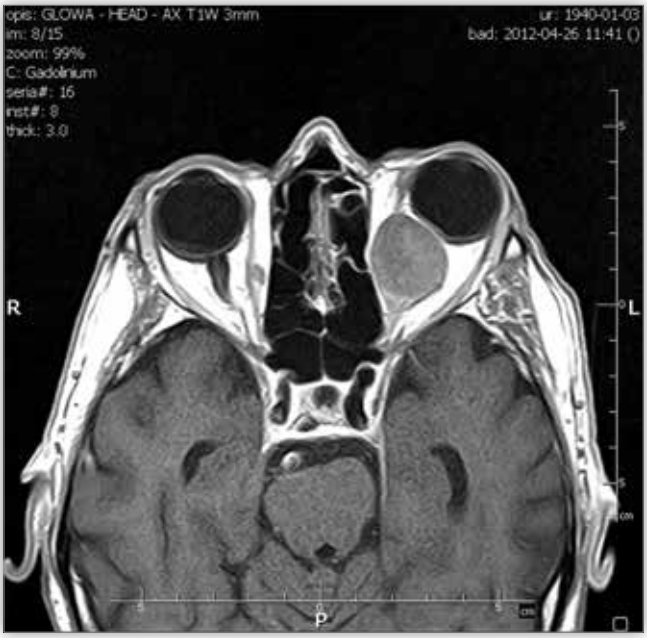

Fig. 6. Large tumor-like lesion compressing the left eye from behind and modeling the lateral aspect of the optic nerve visualized on T1-weighted MRI image in axial cross-section. A small lesion located medially from the medial rectus muscle may be observed in the right orbit. A small hyperintense focus, possibly corresponding to metastasis, is visible in the region of right sphenoid sinus.

Ryc. 6. Obraz T1-zależny rezonansu magnetycznego w przekroju osiowym – widoczne sa: duża zmiana guzowata uciskająca z tyłu gałkę oczną lewą i modelująca do boku nerw wzrokowy, w oczodole prawym niewielka zmiana leżąca przyśrodkowo przy mięśniu prostym przyśrodkowym, w okolicy prawej zatoki klinowej niewielkie hiperintensywne ognisko – meta?

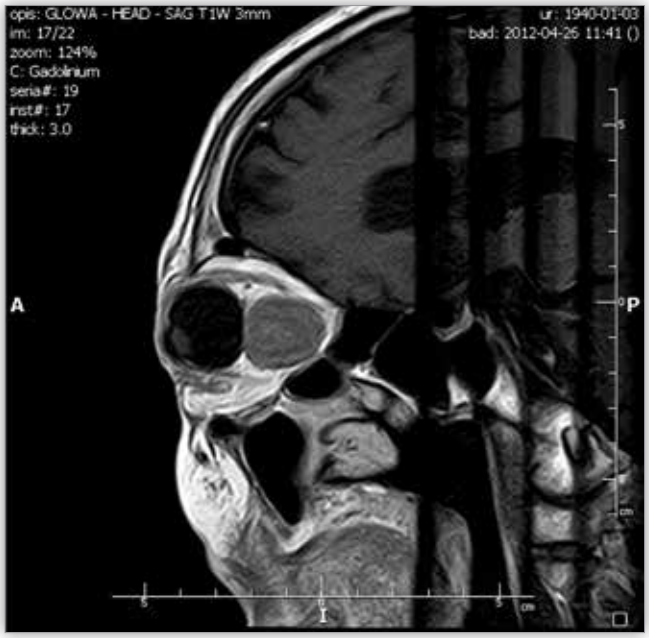

Fig. 7. Large tumor-like lesion compressing the left eye from behind visualized on T1-weighted MRI image in sagittal cross-section.

Ryc. 7. Duża zmiana guzowata uciskająca z tyłu gałkę oczną lewą – widoczna w obrazie T1-zależnym rezonansu magnetycznego w przekroju strzałkowym.

defined, with even, smooth contours. It compresses the eye and has displaced it anteriorly, with no signs of infiltration;

additionally, it compresses the optic nerve laterally. A small lesion with similar morphology, 4 x 5 x 4 mm in size, may be observed at the medial edge of the medial rectus muscle in the right eye, possibly corresponding to metastasis (Fig. 6 and 7).

Furthermore, 8 x 7 x 8 mm focus with enhanced signal in T2-weighted and FLAIR images, and upon contrast agent administration, was detected in the medial part of the right temporal lobe, next to the wall of Meckel's cavity and sphenoid sinus. Similar lesions, about 8 mm in diameter, were visualized as a linear enhancement in the right temporal region at the level of Sylvian fissure, and on the vault of the right parietal region. Such MRI images might correspond to metastatic lesions.

Chest radiography

Numerous, round shadows of variable size were detected in pulmonary fields, probably corresponding to metastases. Additionally, a tumor like lesion (7 x 8 cm) was visualized in the upper pole of the left pulmonary hilum.

Computed tomography of the chest

A large tumor-like lesion, 65 x 70 x 65 mm (RL x HF x AP) may be observed in the second segment of the left lung. The tumor has heterogeneous, solid-cystic structure, with hypodense areas probably corresponding to decay zones. It is adjacent to the long section of the proximal segment of descending aorta surrounding about one half of its diameter, with possible infiltration. Additionally, the mass is segmentally adjacent to the division of pulmonary and inferior lobe artery. Slightly smaller tumor-like lesion, 50 x 40 mm in size, and with similar morphology was observed at the level of the left pulmonary hilum, probably corresponding to the conglomerate of enlarged lymph nodes.

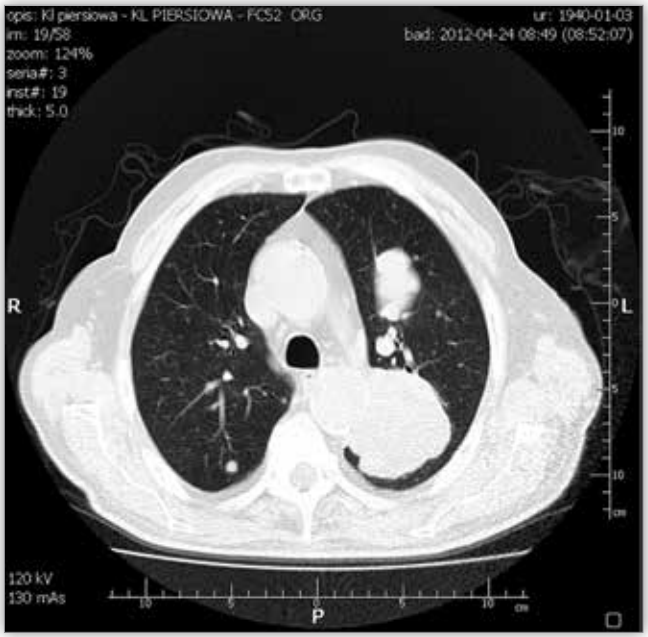

Fig. 8. Large tumor-like solid-cystic lesion adjacent to the descending aorta, along with smaller tumor-like lesions spread within both lungs, visualized on T1-weighted CT scan in axial cross-section.

Ryc. 8. Duża zmiana guzowata lito-torbielowata przylegająca do aorty zstępującej oraz mniejsze zmiany guzowate rozsiane w obu płucach – widoczne w obrazie T1-zależnym tomografii komputerowej w przekroju osiowym.

Moreover, numerous, disseminated, smaller tumor-like structures varying in size may be observed in both lungs (Fig. 8). Based on the CT findings, the largest tumor-like structure in the left upper pulmonary lobe probably corresponds to the primary malignancy, surrounded by numerous metastatic foci. Additionally, enlarged lymph nodes may be observed in the mediastinum: subcarinal lymph node (17 x 15 mm), and the lymph node of the right pulmonary hilum (17 x 13 mm), as well as the enlarged axillary lymph node on the left side, 17 mm in diameter.

Abdominal ultrasonography

Pancreas not enlarged, with a cystic area 5 mm in diameter, at the border of the pancreatic corpus and tail. Also, liver not enlarged, with hyperechogenic 20 x 15 mm area (Fig. 9) in the left lobe. Cortical cysts detected in the right kidney: 66 mm in diameter in the inferior pole, and 28 mm in the superior pole. Additionally, two isolated sinal cysts detected in the left kidney, 12 mm and 8 mm in diameter, respectively, along with a hyperechogenic area 16 x 14 mm in adrenal field.

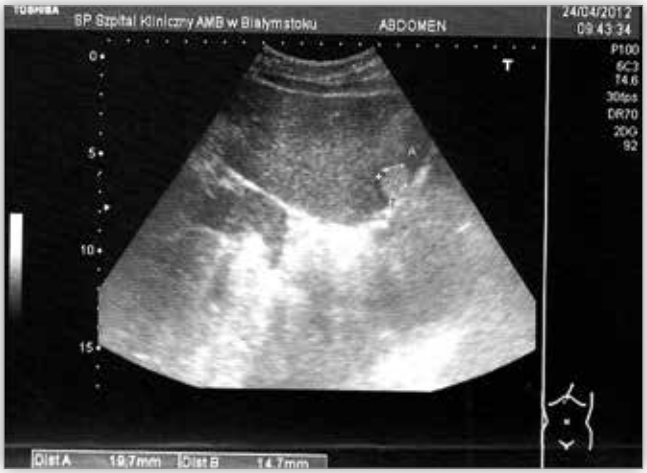

Fig. 9. Ultrasonographic image of the tumor-like lesion (19.7 x 14.7 mm) of the left hepatic lobe.

Ryc. 9. Guzowata zmiana o wielkości 19,7 x 14,7 mm, umiejscowiona w lewym płacie wątroby – obraz ultrasonograficzny.

Computed tomography of abdominal cavity

Tumor-like solid structures detected in both adrenal glands, enhanced upon contrast agent administration. The sizes of the left and right adrenal lesions: 35 x 35 mm and 25 x 17 mm, respectively; both of metastatic character. Additionally, hypodense focal lesion 18 x 14 mm in size detected next to the diaphragm, in segment II-III of the left hepatic lobe, probably corresponding to metastasis.

Gastroscopy

Esophagus and gastric and duodenal mucosa are normal.

Colonoscopy

Both the large intestine and ileum are normal.

Aside from diagnostic imaging, the basic blood and urine laboratory parameters, as well as tumor markers, were determined in the patient. The following abnormalities were documented: level of CA 19–9 XR marker increased to 71.04 U/mL

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(norm: 37 U/mL), leukocytosis of 16.72 x 10^3 μL (norm: 4–10 x 10^3 μL), slight decrease in hemoglobin concentration to 13.4 g/dL (norm: 14–16 g/dL), abnormalities in albumin fraction, amylase activity elevated to 102 IU/L (norm: 0–90 IU/L), CRP level equal to 12.1 mg/L (norm: 0–10 mg/L), and ESR equal to 43.

After consultation with pulmonologist, thoracic surgeon, and oncologist, thin needle biopsy of the lesion located in the left lung was ordered. The cells of small cell lung carcinoma were detected in the biopsy specimen.

On the basis of the complete clinical examination, and particularly the histopathological examination of biopsy specimen obtained from the left lung, the diagnosis of disseminated malignancy was established, with the primary lesion most probably located in the lung. Due to the type of malignancy, i.e. small cell lung carcinoma with numerous lymph node metastases, as well as the metastases to the brain, liver, adrenal glands, and both orbits, the patient was qualified to oncological treatment comprised of radio- and chemotherapy. After only one week of intensive diagnostic procedures at the Clinic of Ophthalmology in Bialystok, the patient was referred for further treatment to the Bialystok Center of Oncology.

Discussion

As suggested by its name, disseminated malignancy is characterized by the presence of many metastases, spread throughout the entire body. However, this is preceded by the period of latency, necessary for the growth of primary tumor and its spread via blood or lymphatic vessels. Clinical manifestations of malignancy are to a large extent determined by its histopathological type and aggressiveness. The most aggressive tumors are characterized by a strong predisposition to hematogenous spread, which occurs rapidly and involves numerous organs. Small cell lung carcinoma constitutes an example of such a malignancy. Up to 75% of patients with newly diagnosed lung cancer already have distant metastases to the brain, adrenal glands, liver, and or bones. Orbital and eye metastases are of extremely rarer evidence. It should be remembered that whenever metastatic orbital tumor of unknown primary location is suspected, it is most likely that the primary lesion is located in the skin (melanoma, 20%), breast (in women; 29%), and prostate (in men; 13%) (1–3). Lung tumors, as well as thyroid, kidney, liver, and intestinal malignancies rarely give rise to orbital metastases (4).

Usually, the spread of malignancy is associated with clinical symptoms, suggesting the involvement of particular organs. Taking the location of primary focus (lung) and metastatic lesions into account, symptoms such as cough, dyspnea, hemoptysis, chest pain, weight loss, general weakness, bone pain, headache and other neurological disorders, as well as nausea, and stomachache should be expected in patient with disseminated small cell lung cancer.

Exophthalmos with associated pain and impaired vision in the involved eye were the symptoms which alarmed our patient, and the only reason to come and see a doctor. Surprisingly, such massive dissemination of lung cancer, confirmed on numerous imaging examinations, was not associated with any other complaints, in particular, with respiratory symptoms.

The results of clinical trials involving patients with metastatic orbital tumors confirm that irrespective of the location of primary tumor, the ophthalmic symptoms can represent the first (although not the only), manifestation of malignancy in about 15–19% of the cases (1, 5). Most frequent ophthalmic abnormalities include exophthalmos with eye displacement (in about 63–75% of patients), double vision (48–54%), elevated intraocular pressure (54%), impaired mobility of the eye (52%), swelling of eyelids and conjunctival hyperemia and chemosis (25–50%), eye pain (28–42%), visual abnormalities (41%), and fundal lesions, such as the swelling of the optic disc and dilatation of venous vessels (17%) (1, 3, 6, 7).

Nevertheless, during our search through the available literature we have found only several case reports in which the ophthalmic manifestations constituted the only sign of developing extraophthalmic malignancy (2, 4, 8); a few of them pertained to the primary pulmonary malignancies (9–14).

On diagnosis, the stage of the disease in our patient was highly advanced due to numerous metastases; consequently, his prognosis was poor. Palliative chemo- and radiotherapy comprise the treatment of choice for this stage. It should, therefore, be asked if earlier detection of malignancy was possible. The lack of clinical symptoms discouraged our patient from visiting a medical professional, other than routine tests associated with the treatment of hypertension and coronary artery disease. Regular chest radiographs seem crucial for the diagnosis of lung cancer in our patient, particularly in view of his long history of smoking, being the principal and most obvious risk factor of lung cancer. Unfortunately, late detection of the disease virtually deprived the patient of the chance to recover. The hereby presented case illustrates that proper prevention is still the most efficient method of cancer control, and tests such as mammography, cytological smears, chest radiography, examination of prostate, and others, should be routinely prescribed to all patients at a relevant age.

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