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CASE REPORTS

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CLINICAL CASE OF NON-TYPICAL METASTASIS OF NEUROENDOCRINE LUNG CARCINOMA TO THE VASCULAR MEMBRANE OF THE EYE

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Background: **Metastases in eye structures are rare (1–5% cases at systemic spread of different malignancies, mainly breast and lung cancers). The prognosis is poor. The overall survival usually does not exceed 12 or even 6 months. If metastases are found in the choroid membrane, the probability that the patient has multiple metastatic lesions of other organs increases significantly. Lung neuroendocrine neoplasms are rare (1–2% of all malignancies in adults), but mainly aggressive tumors. They are characterized by "blurred", nonspecific clinical symptoms, the correct diagnosis is delayed seriously, and distant metastases are seen in more than 40% of patients (usually in chest structures, liver, bones, brain, and adrenal glands; metastasis to vascular membrane of the eye ranks the 6th place).** ***Case report:*** **Own clinical observation of a male patient with rare metastasis of lung neuroendocrine carcinoma to the choroid of the left eye is presented. The disease is manifested by an ocular metastasis, which was initially considered an embryonic tumor. Other metastatic lesions (hilar lymph nodes, liver, soft tissues) were detected on computed tomography a little bit later. The diagnostic algorithm using routine histological examination and immunohistochemistry, including detection of neuroendocrine markers (chromogranin A, synaptophysin), cytokeratin 7 and Ki-67 expression in primary and metastatic tumors is described.**

Key Words: **lung neuroendocrine carcinoma, ocular metastasis, morphological diagnostics, immunohistochemistry.**

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Neuroendocrine neoplasms (NENs) is a group of rare heterogeneous malignancies that originate from cells of the diffuse neuroendocrine system. They are characterized by different histological features, malignant potential, differences in clinical course and prognosis. NENs are found most often in the gastrointestinal tract (in 62–67% cases) and lungs (22–27%) [1–3]. The frequency of NENs detection over the past 30–40 years has increased from 1.09 to 6.98 per 100 thousand population per year, mainly due to improved methods of morphological and complex diagnostics [2, 4].

According to the literature data, NENs do not exceed 0.5–6% in the structure of general oncological morbidity. Broncho-pulmonary NENs account for 1–2% among all malignancies in adults and up to 20–30% of all NENs [3, 5–8].

Broncho-pulmonary NENs are rather heterogeneous. According to histological features, proliferative activity and clinical course they are classified into 4 main subtypes (Fig. 1): typical and atypical carcinoid (respectively highly and moderately differentiated neuroendocrine tumors (NETs), and low-differentiated large- and small-cell neuroendocrine carcinomas (NECs) [3, 9, 10]. However, such classification is not final, because sometimes well-differentiated NETs are more similar in their course to aggressive NECs [3, 11]. All NETs are considered potentially malignant and able to metastasize [12]. Thus, typical carcinoids metastasize to regional lymph nodes in 10–15% cases and only in 3% distant metastatic lesions are seen (liver, brain, adrenal glands or bones). Atypical carcinoids are diagnosed with metastasis in about 20% of patients [13].

Almost 40% of bronchopulmonary NENs show non-neuroendocrine histological elements. Lung adenocarcinomas including more than 30% of neuroendocrine component are considered NECs [3].

At least 40% of patients with NENs at the time of diagnosis have regional or distant metastases, and quite often metastatic lesions are multiple, so prognosis is poor [3, 14–17].

Usually lung malignancies metastasize to chest structures, liver, bones, brain, adrenal glands. Metastasis to the vascular membrane of the eye ranks the 6th place [18–20].

Distant metastases in lung NENs at the time of diagnosis are detected in more than 40% of cases (liver lesion — 19%, bones — 14%, central nervous system — 9%, other locations — about 15%). Almost 10% of patients with bronchopulmonary NENs have metastatic brain damage, but metastases in the central nervous system structures are not typical for NENs of other locations [16, 21].

Eye structures represent a rare location for metastases of malignant tumors (1–5% cases at their

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Abbreviations used: Chr A – chromogranin A; CK7 – cytokeratin 7; CT – computed tomography; IHC – immunohistochemistry; NEC – neuroendocrine carcinoma; NEN – neuroendocrine neoplasm; NET – neuroendocrine tumor; Syn – synaptophysin.

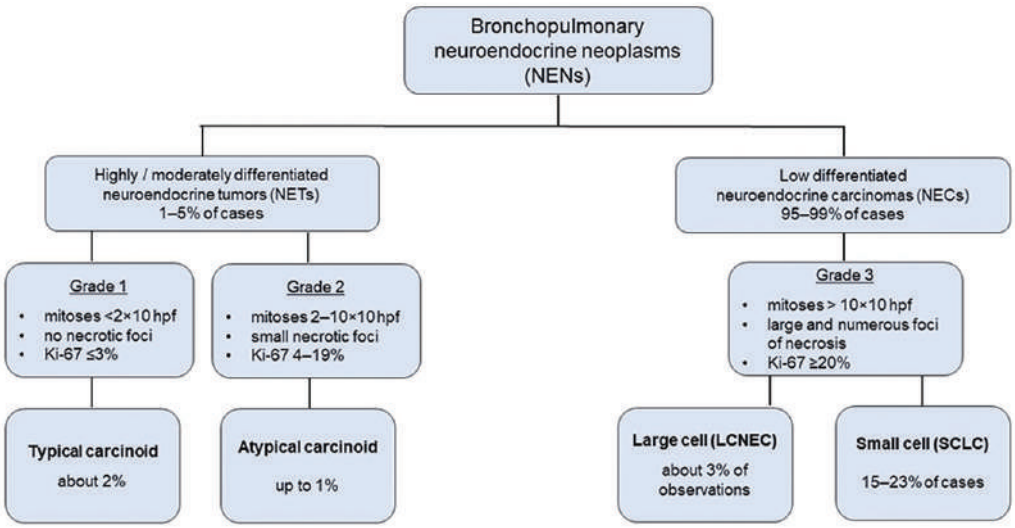

Fig. 1. Generalized scheme of classification of bronchopulmonary NENs into 4 histological subtypes with incidence of each subtype (adapted from [1, 10])

systemic spread). In addition, such lesions significantly impair the life quality and shorten the overall survival of patients, which, according to various literature sources, usually does not exceed 13–22 months (sometimes 4–6 months), despite the histological type of primary malignancy [22–24].

According to retrospective studies, in 24–34% of patients orbital metastasis was the first clinical sign of a malignant tumor with dissemination. In almost 90% of cases, orbital metastases were unilateral, more often on the left side [17, 18, 25–27]. Metastatic lesions of the eye structures usually affect the vascular membrane (almost 80% of observations), the iris (10%) and ciliary body (2%). Choroidal metastases are most often seen in breast cancer (about 55% of cases), lung malignancies (16–20%), melanoma of the skin (4.5%), prostate tumors (3.6%) and neoplasms of the gastrointestinal tract (3.6%). In pediatric patients, neuroblastoma mostly metastasizes to the eye structures [24, 26]. According to the literature data, in 0.7–12% of patients with lung cancer, orbital metastases originate due to hematogenous tumor dissemination [25]. The choroid membrane is supplied from a large blood vessel — ciliary posterior artery, in addition, choroidal vessels have numerous anastomoses, which contributes to the hematogenous spread of metastases. If metastases are present in the choroid membrane, the probability that the patient has multiple metastases in other organs increases significantly [18, 19].

Metastatic lesion of the eye structures is usually accompanied by diplopia, blurring or loss of vision, impaired visual fields, photopsia, sometimes protrusion of the eyeball, with its reduced mobility, and pain. However, about 11–23% of such lesions remain asymptomatic for a long time [19, 28].

Our own clinical observation of bronchopulmonary NEC metastasis to the vascular membrane of the eye is presented.

CLINICAL CASE

Patient B., male, aged 54, was hospitalized on 23.11.2020 at the Filatov Institute of Eye Diseases and Tissue Therapy, NAMS of Ukraine, with complaints of pain and impaired movements of the left eye. Based on the examination the following diagnosis was made: melanoma of posterior choroid, secondary glaucoma. On 25.11.2020, the surgery was performed — left eye was enucleated. Non-pigmented tumor of posterior chamber of the eye was detected histologically. On the section, which covered the anterior-equatorial and posterior parts of the eye, a nodular tumor with radiation into the eye cavity up to 8 mm and spread along the choroid up to 14 mm was visualized.

According to microscopic examination, the tumor mostly consisted of the primitive (medullary) neuroepithelium as well as numerous perivascular pseudorosettes with foci of necrosis and hemorrhage. Due to the lack of information about probable metastatic lesions at the time of examination, the tumor was considered by pathologists as the primary intraocular neoplasm of neuroepithelial origin — medulloepithelioma. In addition, nodular type of growth with high radiance into the eye cavity is atypical for metastatic tumors, which often show a flattened (lenticular) growth, mainly along the choroid with low radiance.

The patient underwent computed tomography (CT) of the chest with dynamic contrast (iopromide). Hypovascular neoplasm in the lower lobe of the right lung with uneven heavy contours 38×70 mm in size was detected. It caused compression of the lower lobe bronchus with its narrowing up to 2 mm, and also segmental bronchi with S6 and S9 amputation. The tumor was fused with a conglomeration of enlarged hilar lymph nodes, which unevenly accumulated the contrast agent. In the right lobe of the thyroid gland a focus 20×30 mm of uneven accumulation of contrast, adjacent to the conglom-

erate of paratracheal lymph nodes, was revealed. In the subcutaneous fat of the anterior chest wall on the right nodular formation 6×7 mm with uneven contours and contrast accumulation on the periphery, was found. In the 5th segment of the liver a hypodense formation 16×22 mm, which unevenly accumulated contrast, was detected. According to CT results, consultation of oncologist, thoracic surgeon, and also bronchoscopy with biopsy were recommended.

On 24.11.2020, the bronchoscopy with the biopsy of the right intermediate bronchus in 4 foci was performed. The posterior wall of the intermediate bronchus was partially stenosed due to a tumor with endophytic peribronchial growth, segment B6 was completely obturated. According to cytological examination, a large number of half-destroyed cells of undifferentiated small cell carcinoma were found. Histological examination: diagnosed with small cell lung cancer. The clinical diagnosis was changed to "Cancer of the right lung, central form".

According to repeated CT of the thoracic cavity with dynamic contrast (after 2 weeks): the picture is similar to the previous one, with negative dynamics. The size of the tumor in the lower lobe of the right lung increased to 50×75 mm, the formation of the subcutaneous tissue of the anterior chest wall — up to 11×14 mm. In addition, in the right lobe of the liver several hypodense foci up to 6 mm with contrast accumulation were found.

On 14.12.2020, the patient was consulted in the Pathological Department of Kyiv City Clinical Oncological Center. Based on results of morphological and immunohistochemical (IHC) examination of formalin fixed paraffin embedded specimens, the diagnosis of small cell lung NEC, Grade 3, with metastasis to the vascular membrane of the eye was made.

Morphological appearance of primary NEC (biopsy) and metastatic specimen (surgical material) was similar: characteristic for NENs trabecular and "rosette-like" structures, small tumor cells with hyperchromatic nuclei and scant cytoplasm. Numerous foci of necrosis and hemorrhage were seen in the tissue of metastatic tumor (Fig. 2).

The cells of both tumors (primary and metastatic) expressed cytokeratin 7 (CK7) and neuroendocrine markers chromogranin A (Chr A) and synaptophysin (Syn); the proliferation index corresponded to Grade 3 (in the primary tumor Ki-67 expression was 80%, in metastatic — 65%) (Fig. 3). Melan A expression was not detected in the vascular membrane of the eye. According to the results of morphological and IHC examination, the identity of the primary and metastatic lesions was confirmed, their bronchopulmonary origin was proved.

Based on a comprehensive examination the patient was diagnosed with small cell NEC of the lungs with metastases to the lymph nodes, soft tissues, liver and vascular membrane of the left eye.

Five months after surgery and 4 months after diagnosis of metastatic lung NEC, the communication with the patient was lost. Repeated surgery was not performed, also, there was no chemotherapy or immunotherapy. The patient died in April 2021 in a private clinic where he received palliative care.

In general, orbital metastases in cancer patients with systemic lesions are found in about 2–3% of cases. And up to 20% of such lesions are caused by metastases of primary bronchopulmonary malignancies [24]. Usually, the clinical manifestations of lung NENs are "blurred", nonspecific, and, despite the diagnostics improvement, more than 50% of patients are diagnosed in III–IV stage by metastases. The prognosis is poor; the average survival rate rarely exceeds 8.3–11 months [16, 29].

It is important to collect the anamnesis data carefully and to stay alert about the potential metastases of malignant tumors, especially breast and lungs (including NENs), if the signs of eye structures lesions are present. If bronchopulmonary NENs metastases are suspected, characteristic "neuroendocrine" architecture and positive expression of neuroendocrine markers (except neuron specific enolase) should be considered, as well

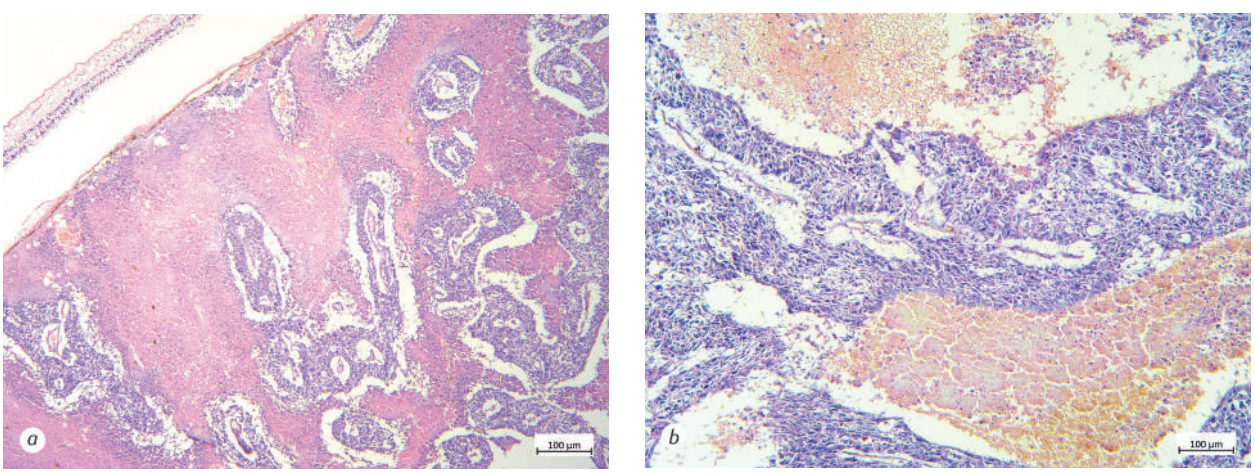

Fig. 2. Metastasis of lung NEC to the vascular membrane of the eye. Small tumor cells with hyperchromatic nuclei and scant cytoplasm form characteristic "rosette-like" structures; numerous foci of necrosis (*a*) and hemorrhage (*b*) in the tumor tissue. H&E staining. ×100 (*a*); ×200 (*b*)

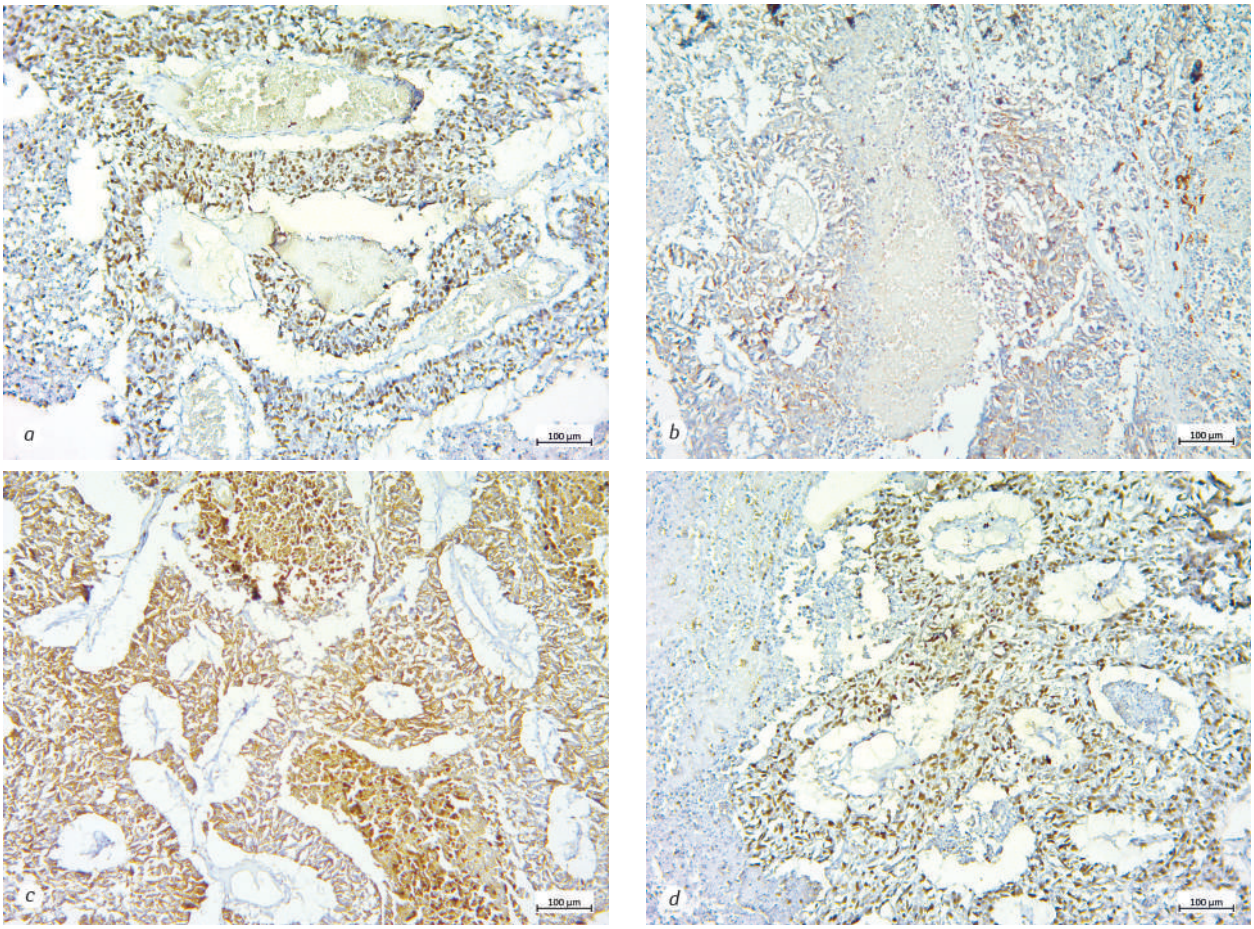

Fig. 3. Metastasis of lung NEC into vascular membrane of the eye. IHC staining: *a* — CK7 positive staining (2+) (monoclonal antibody anti-human CK7, clone OV-TL 12/30; Dako, Denmark), ×200; *b* — Chr A week positive staining (1+) (monoclonal antibody, clone SP12, Invitrogen, Thermo Fisher Scientific, USA), ×200; *c* — Syn positive staining (2+) (monoclonal antibody, clone DAK-SYNAP; Dako, Denmark), ×200; *d* — Ki-67 expression 65% (monoclonal antibody anti-Ki-67, clone MIB-1; Dako, USA), ×200

as CK7 (for differential diagnosis with gastrointestinal NENs). The diagnostics should be complex, including IHC, CT or MRI as there is a high probability of distant metastases of lung NENs.

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КЛІНІЧНИЙ ВИПАДОК НЕТИПОВОГО МЕТАСТАЗУ НЕЙРОЕНДОКРИННОЇ КАРЦИНОМИ ЛЕГЕНІ В СУДИННУ ОБОЛОНКУ ОКА

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Метастази в структурах ока виявляють рідко (1–5% за системного розповсюдження при різних онкологічних захворюваннях, найчастіше при раку молочної залози і легені). Прогноз зазвичай несприятливий. Загальна виживаність, як правило, не перевищує 12 або навіть 6 міс. При виявленні метастазів у судинній оболонці ока ймовірність множинного метастатичного ураження інших органів суттєво зростає. Нейроендокринні новоутворення легені — рідкісні (1–2% всіх злоякісних новоутворень у дорослих), але переважно агресивні пухлини. Для них характерні «стерті», неспецифічні клінічні прояви, встановлення правильного діагнозу суттєво відтерміноване, віддалені метастази наявні у понад 40% пацієнтів (зазвичай в органах грудної порожнини, печінці, кістках, головному мозку, надниркових; метастази в судинну оболонку ока посідають 6-те місце за частотою). ***Клінічний випадок***. Наведене власне спостереження пацієнта при нейроендокринній карциномі легень з рідкісним метастазом у судинну оболонку лівого ока. Маніфестація захворювання — метастаз в око, який спочатку був розцінений як ембріональна пухлина. Інші вогнища метастатичного ураження (внутрішньогрудні лімфатичні вузли, печінка, м'які тканини) виявлені дещо пізніше за даними КТ. Описаний діагностичний алгоритм з використанням рутинного гістологічного та імуногістохімічного досліджень, включаючи визначення експресії нейроендокринних маркерів (хромогранін А, синаптофізин), цитокератин 7 і Ki-67 у первинній і метастатичній пухлинах.

Ключові слова: нейроендокринна карцинома легені, метастаз в око, морфологічна діагностика, імуногістохімія.