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Ocular manifestations of lung cancer

Anna Brzecka[1], Maria Ejma[2], Marta Misiuk-Hojło[3]

Cancer may affect the eye by remote paraneoplastic effects, indirectly by infiltration or compression of nerves, and by local or distant metastases. Non-metastatic retinopathy related with lung cancer, called CAR (cancer-associated retinopathy), is an autoimmune disorder, caused by the remote effects of cancer on the retina and leads to rapidly progressive visual loss. The autoantibodies that cause CAR bind to a retinal protein called recoverin. The other presentations of paraneoplastic syndromes involving eyes include encephalomyelitis, Lambert-Eaton syndrome, cerebellar degeneration, and opsoclonus/myoclonus. These syndromes most frequently occur in association with small-cell lung cancer. Lung cancer may also indirectly involve the eyes due to infiltration of the cervical sympathetic chain, causing Horner's syndrome due to lung cancer (usually non-small cell cancer) located in the apex of the lung. The disturbances of the function of cranial nerves may develop because of neoplastic meningitis or, occasionally, of isolated metastases of cranial nerves in the course of lung cancer. Metastases of the lung cancer to the eye and orbit occur very rarely and the metastatic tumor to the uvea is the most common form of an intraocular malignant process.

Oczne objawy raka płuca

Rak płuca może wywoływać oczne objawy związane z zespołami paranowotworowymi, naciekaniem lub uciskiem nerwów okoruchowych oraz miejscowymi bądź odległymi przerzutami. Paranowotworowym zespołem, rozwijającym się w przebiegu raka płuca, jest autoimmunologiczna retinopatia, nazywana CAR (cancer-associated retinopathy), która szybko prowadzi do utraty wzroku. Autoprzeciwciała, wywołujące CAR, wiążą się z białkiem siatkówki, nazywanym rekoweryną. Do innych zespołów paranowotworowych, wywołujących objawy oczne w przebiegu raka płuca – najczęściej drobnokomórkowego należą zapalenie mózgu i rdzenia kręgowego, zespół Lamberta-Eatona, zwyrodnienie móżdżkowe oraz zespół mioklonii – opsoklonii. Rak płuca (zwykle niedrobnokomórkowy rak szczytu płuca) może wywoływać zespół Hornera, w następstwie naciekania szyjnego pnia współczulnego. Do powstania ocznych objawów w przebiegu raka płuca może prowadzić uszkodzenie nerwów czaszkowych, spowodowane nowotworowym naciekaniem opon mózgowo-rdzeniowych lub – wyjątkowo – przerzutami do nerwów czaszkowych. Bardzo rzadko zdarzają się przerzuty raka płuca do oka (zwykle do błony naczyniowej oka) lub do oczodołu.

Key words: lung cancer, paraneoplastic syndromes, CAR
Słowa kluczowe: rak płuca, zespoły paranowotworowe, CAR

Cancer may affect the eye by remote paraneoplastic effects, indirectly by infiltration or compression of nerves, and by local or distant metastases. Paraneoplastic syndromes and symptoms associated with lung cancer encompass several distinct clinical and pathologic entities.

Cancer-associated retinopathy

The non-metastatic retinopathy related with cancer is usually referred to as CAR (*cancer-associated retinopathy*) [1]. This is a rare syndrome that predominantly occurs in patients with small cell lung cancer [2-4], although its occurrence with non-small cell lung cancer [5] has been described. The other neoplastic diseases may also lead to CAR [6-9]. The eye autopsy examination of patients with CAR has revealed patchy losses of photoreceptors of the extramacular retina and relative sparing of cones; there may even be complete absence of the retinal neurones involved in phototransduction [10].

CAR is an autoimmune disorder probably caused by the remote effects of cancer on the retina or optic nerve [1]. The autoantibodies that cause CAR specifically bind to the photoreceptor-specific, calcium binding 23-kD retinal protein called recoverin [1, 3, 11-15]. This protein can be found in rods and cones, and – interestingly – also in small-cell lung cancer cells [16]. However, the serum of the patients with CAR may contain not only antibodies against recoverin, but also against other retinal proteins,

[1] Department of Lung Diseases
[2] Department of Neurology
[3] Department of Ophthalmology
University Medical, Wrocław

e.g. of 34 kD [8], 46 kD [17], 60 kD [4], 65 kd [7] or 70 kD [14], as well as against enolase [18], or neurofilaments [14]. Thus, the absence of antibodies aimed at the 23 kD protein does not exclude the diagnosis of paraneoplastic retinopathy.

The main symptom of CAR is initially mild and moderate, and then rapidly progressive, often asymmetric, bilateral visual loss, which may lead to complete blindness [4, 9, 18]. Other complaints include photosensitivity, night blindness, impaired colour vision, light-induced glare, flashing lights or ring, paracentral, and mid-peripheral scotomas [3, 9, 18].

Ophthalmologic examination may reveal visual deterioration, optic disc pallor, narrowing of the retinal arterioles and clumbing of the retinal pigment epithelium [4, 9, 11]. The retinal changes are focal and visual field defects are often heterogeneous [9].

Fluorescein angiography reveals progressive diminution of peripheral retinal blood flow, slow perfusion and staining of venules [5]. Electrooculography shows reduced light peak/dark trough ratio [19]. Electroretinography demonstrates reduced amplitudes of the cone and rod-mediated responses [7, 11]. Although the results of ophthalmologic examination are not specific for CAR, it is postulated to consider the triad of symptoms: photosensitivity, ring scotomatous visual field loss and attenuated retinal arteriole calibre highly suggestive of CAR [11]. The study of visual evoked responses shows waves either markedly reduced in amplitude or non-recordable [19]. Demonstration of antirecoverin antibody in a patient with signs of retinopathy establishes the diagnosis [15].

CAR is usually observed before the diagnosis of primary cancer [4, 5, 11]. In rare cases CAR can be recognised after the primary malignancy was found [3]. Rising antibody titers to the cancer-associated retinopathy antigen probably occurs before progressive visual field loss and may be considered an indication for prompt therapy [2]. More than half of the patients with CAR have been reported to respond with visual improvement after systemic steroid therapy [2]. Prednisone treatment appeared to reduce the patient's antibody titers to normal [2]. Combined therapy with oral corticosteroids and plasmapheresis may result in a recovery of vision [4]. Intravenous immunoglobulin may be another treatment option offered to patients with paraneoplastic visual loss [18].

Primary tumor treatment (surgical and/or cytotoxic), optionally combined with corticotherapy (optionally with plasmapheresis) may cause slight (and/or transitory) visual improvement in some patients with CAR [4, 5].

Predominantly neurologic paraneoplastic syndromes with ocular involvement

Paraneoplastic neurologic and ophthalmologic dysfunctions accompanying lung cancer may present as encephalomyelitis, Lambert-Eaton syndrome, cerebellar degeneration, and opsoclonus/myoclonus; these paraneoplastic syndromes most frequently occur in association with small-cell cancer [20].

The characteristic pathological feature of paraneoplastic encephalomyelitis is inflammation, perivascular lymphocytic infiltration, and neuronal loss in diverse regions of the central nervous system, including the brain stem, hippocampus, spinal cord and dorsal root ganglia. The anatomic site of inflammation determines the clinical presentation (memory loss, behavioural changes, seizures, weakness, dysarthria, nystagmus, autonomic nervous system dysfunction). The presence of small cell lung cancer, predominating neurological symptoms with normal CT scans, and the presence of anti-Hu antibodies may help to establish the diagnosis [21].

Paraneoplastic cerebellar degeneration is a clinical syndrome of subacute, progressive ataxia, which occurs secondary to degeneration of the Purkinje cells of the cerebellar cortex. It may be associated with small cell lung cancer [22]. Clinical features include ataxia, dysartria, vertigo and ocular manifestations – nystagmus and diplopia [23]. The cerebrospinal fluid shows mild pleocytosis, elevated protein and oligoclonal bands. Anti-Purkinje cell (anti-Yo) antibodies are detected in the serum or in the cerebrospinal fluid of 50% of patients. The anti-Yo antibody appears to be specific for paraneoplastic cerebellar degeneration associated with gynecologic (breast and ovarian) cancer.

The Lambert-Eaton syndrome afflicts up to 5% of patients with small cell carcinoma and occurs much less frequently in patients with non-small cell carcinoma [24]. Neurological symptoms usually precede the diagnosis of malignancy and usually include proximal lower and/or upper limb weakness, depressed tendon reflexes and autonomic dysfunction – especially dryness of the mouth [25]. The Lambert-Eaton syndrome can also have ocular manifestations; these include mild/moderate ptosis (in 54% of cases), rarely enhanced ptosis, diplopia, blepharoptosis, blurred vision, abnormal pupil responses to light and parasympathetic and sympathetic denervation hypersensitivity of the iris musculature and ophthalmoplegia [25-27].

Weakness and autonomic dysfunction in the Lambert Eaton myasthenic syndrome may be controlled by 3,4-diaminopyridine; intravenous immunoglobulin or plasmapheresis may also provide short-term improvement in severely affected patients. Prednisolone is indicated in patients who fail to respond sufficiently to symptomatic treatment [28]. A combined treatment approach with the use of chemotherapy and radiotherapy in small-cell lung cancer, or surgery, radiotherapy and/or chemotherapy i non-small cell lung cancer together with pharmacological treatment of neurological symptoms usually results in a certain improvement [29].

Opsoclonus is a dyskinesia consisting of involuntary, arrhythmic, chaotic, multidirectional saccades, without intersaccadic intervals. It is usually associated with arrhythmic-action myoclonus that predominantly involves the trunk, limbs and head [30-32]. This syndrome, also known as the "dancing eyes" and "dancing feet" syndrome,

is associated with cancer in about 20% of adults, usually with small cell lung carcinoma and, more rarely, with non-small cell carcinoma [31]. The onset of this disorder is subacute and precedes the tumour diagnosis [31].

The opsoclonus/myoclonus paraneoplastic syndrome is sometimes associated with a specific "anti-Hu" antineuronal antibody [30]. This antineuronal nuclear autoantibody (also known as ANNA-1) is a marker of neurologic autoimmunity, which is evidently associated with small-cell lung carcinoma [33]. This antibody stains the nucleus and cytoplasm of all neurons, and reacts with a group of 35- to 40-kd proteins in neuronal immunoblots [34]. The protein targets of ANNA-1 belong to a family of RNA-binding proteins which probably regulate posttranscriptional processing of RNA [34].

Lung cancer indirectly involving eyes

The Pancoast syndrome (or superior pulmonary sulcus tumor) is associated with bronchogenic carcinoma located in the apex of the lung; it produces a characteristic clinical syndrome of neuropathic pain of the upper extremity and Horner's syndrome. Horner's syndrome is a consequence of the involvement of the cervical sympathetic chain and consists of ptosis and the signs of sympathetic ocular paralysis [35]. A majority of Pancoast tumors are non-small cell lung carcinoma, but small cell lung carcinoma and metastatic lesions from a variety of pulmonary and non-pulmonary malignant tumours may produce an identical picture [35].

Metastases of lung cancer causing ocular symptoms

Neoplastic neural damage may be caused by extrinsic compression of a tumour or infiltration of malignant cells along the nerves of the meningeal layers. Metastases to the cranial nerves rarely occur as an isolated form; this process represents in fact a diffuse cancerous meningoradiculitis involving the cranial nerves. Neoplastic processes may affect every cranial nerve. Most patients had multiple cranial nerve involvement with the fifth and sixth nerve being the most common site of disease. Neoplastic meningitis occurs in 10-26% of patients with lung carcinoma [36]. When cancer cells enter the subarachnoid space they spread along the leptomeninges, surround or invade nerve roots, form perivascular cuffs and enter the Virchow-Robin spaces or penetrate the pia matter, thus involving the superficial layers of the central nervous system parenchyma. Diffuse infiltration of the leptomeninges is a characteristic pattern of tumour growth. Neoplastic meningitis is pleomorphic in its clinical presentation. There are neurological disturbances of cerebral hemispheres (headache, mental status changes, seizures, ataxia), cranial nerves (double vision, hearing loss, facial numbness, loss of vision), and spinal cord and roots symptoms (leg and arm weakness, numbness and pain).

Lung cancers rarely metastasize to the eye, but metastatic orbital disease is situated as the third most frequent malignancy (21%), after breast carcinoma (29%) and neuroblastoma (25%) [37]. Metastatic tumor of the uvea is the most common form of an intraocular malignant process; metastases to the ciliary body, iris, retina, optic disc, and vitreous are rare [17]. Proptosis (68%), motility disturbance (57%) and mass (50%) are the three most common presenting signs of lung metastases into the eye and orbit [37].

Dr n. med. Anna Brzecka
Katedra i Klinika Chorób Płuc AM
Grabiszyńska 105, 53-439 Wrocław
e-mail: aniabrz@box43.pl

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