Coexistence of an active form of tuberculosis and non-small cell lung cancer with metastases to the eyeballs

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It is known that patients with tuberculosis in anamnesis have an increased risk of lung cancer development. Shorter survival of patients with diagnosed lung cancer preceded by an active form of tuberculosis has also been stated. On the basis of data accessible in the literature, a close relation between these two morbidities is observed. The question of which disease develops first is still unanswered. There are studies suggesting that tuberculosis might support cancer development by evoking an inflammatory reaction and fibrosis in involved tissue, leading subsequently to neoplastic transformation. Adversely, other studies claim that lung cancer is a risk factor of tuberculosis, probably by causing immunity decrease, which increases the risk of new infection development or reactivation of an old one.
In our study, a case of 61-year-old woman with diagnosed tuberculosis in the course of non-small cell lung cancer treated with chemotherapy is presented. The tuberculosis was diagnosed on the basis of positive bacteriological findings in material obtained during a bronchofiberoscopy and a positive result of a QuantiFERON TB-Gold test in blood serum. The depicted case confirms that the coexistence of tuberculosis and lung cancer worsens the patient's prognosis, causes significant problems with diagnosis and impairs the effectiveness of cytostatic treatment.

Key words: non-small cell lung cancer, lung tuberculosis, chemotherapy effectiveness.

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Case report

In April 2010, a 61-year-old female with complaints of two months' visual acuity that was worsening was admitted to an ophthalmological ward. She declared no complaints from the respiratory tract or other organs. She had been smoking 35 cigarettes a day for 35 years. Her family history revealed non-small cell lung cancer in her sister. During hospitalisation, an intraocular tumour and a secondary retinal detachment in the left eye as well as thyroid nodules were diagnosed. Laboratory tests did not reveal any abnormalities. An ultrasonography (USG) of the thyroid gland, which was also performed, visualised two well restricted, non-homogenous, hypoechogenic lesions in the right lobe and bilateral enlarged lymph nodes on the neck, the larger one in the supraclavicular area. In a fine needle aspiration biopsy of the thyroid gland, no atypical cells were found. Chest X-ray disclosed a patchy density in the lower part of the pulmonary hilus and a shallowness of the left costophrenic angle. Abdominal USG, gynaecological examination and head CT did not reveal any pathology. In orbital USG, the tumour mass in the posterior pole of the left eyeball, which did not exceed the eyeball wall, was exposed. No pathology was found in the right eye or orbit.

For the purpose of further diagnosis and treatment, the patient was referred to the Department of Ophthalmology of the Poznan University of Medical Sciences. During the hospitalisation in June 2010, MRI of the orbits was performed and a choroidal tumour with a total serous retinal detachment, localised in the posterior pole of the left eye, was shown. Furthermore, a lentiform tumour mass with a similar signal and intensity as in the left side, was detected in the fundus of the right eye. No extraocular penetration of the intraocular lesions was stated. The picture aroused suspicion of metastasis to the eye or primary choroidal melanoma. MRI of the entire body was ordered. Within the spine in the L3, L4 and L5 vertebral body, neoplastic changes were revealed. Two similar lesions were demonstrated in the left iliac bone shaft. In the inferio-posterial side of the right pulmonary hilus, in the direction of the 6th and 7th bronchopulmonary segment, a diffused solid lesion 40 × 45 mm in size and a small amount of fluid in the transverse fissure of the right lung was found.

The patient was transferred to a pulmonology department in another hospital, where chest CT was performed. In the 4th segment the examination revealed an infiltrating lesion, of which the transverse dimension was 43/22 mm. Spirometric examination revealed mild degree obstruction of the bronchi. Bronchofiberoscopy was performed, and samples of tissues were

obtained for examination. On the basis of histopathological examination, non-small cell carcinoma of the right lung was recognised. The lesions in bones and eyeballs were defined as metastases.

Further treatment was provided in the Department of Pulmonology, Allergology and Pulmonary Oncology in Poznan, where, on the basis of previously executed tests, the neoplastic disease was qualified as being 4th stage in the patient in good clinical statement (PS-I according to the ECOG scale). In the physical examination, blindness of the left eye and amblyopia of the right one and slightly hypoacoustic normal vesicular sound were stated.

Palliative radiotherapy of the iliac bone and four cycles of chemotherapy (PN scheme – cisplatin and vinorelbine) were instituted in the period from July to October, 2010. After the first cycle of chemotherapy, an ophthalmological examination was performed in the Ophthalmological Department of Poznan University of Medical Sciences. In the posterior pole of the right eye, above the upper temporal arcades, an amelanotic choroidal tumour, of appearance typical for metastasis, was revealed. In the left eye a total serous retinal detachment with a tumour mass situated in the posterior pole and around the optic disc was also visible. The patient showed good tolerance to cytostatic treatment, which was complicated by mild degree anaemia and two days of vomiting after the fourth cycle of chemotherapy.

In control chest CT, after the second cycle of chemotherapy, a decrease in the tumour dimension of the right lung to 29/17 mm was detected. In MRI of the orbits no lesions were revealed. After ophthalmological examination, significant regression of the lesions in both eyes was stated. The effectiveness of the treatment was assessed again a month after the fourth cycle of chemotherapy – in December 2010 in the Pulmonological Department. In executed imaging results, the tumour remission was confirmed. A decision of radiotherapy implementation was made. In January 2011 the patient achieved treatment of 20 Gy/T dose to the mediastino-pulmonary right side.

A consecutive estimation of the disease advance was conducted in March 2011 on the basis of performed imaging examinations. Although chest CT revealed stabilisation of the disease, an MRI of the orbits showed recurrence of lesions in both eyes with marked progression. Therefore, the decision of second-line chemotherapy (docetaxel) was made.

During the hospitalisation, in April 2011, control endoscopic examination of the respiratory tract was performed and Mycobacterium tuberculosis complex was identified in a bacterial culture (a positive bacteriological finding of bronchial washings after 21 days). Additionally, the specific process was confirmed by a positive result of a QuantiFERON-TB Gold test in blood serum.

The cytostatic therapy was continued in association with the antituberculotic treatment (Nydrazid, Rifampicin, Pyrazinamid), which was well tolerated by the patient. The effectiveness of the prescribed therapy was assessed during control tests. A chest CT from the beginning of May 2011 showed a significant slide of the tumour dimensions in the right lung, connected with a spread decrease of parenchymal infiltrations in the direct proximity of the tumour and resorption of fluid from the right pleural cavity. In a performed ophthalmological examination, visual acuity improvement and complete regression of metastases in both eyes were stated.

It seems that the applied therapy was characterised by marked effectiveness; however, the confrontation with lung CT image (June 2011) verified this outlook. Changes in the character of the peribronchial condensations in the 3rd, 4th and 8th segment of the right lung and fibrosis within the lingula and the apex of the left one, showed significant disease progression. After ophthalmological consultation, which confirmed stabilisation within the eye with no tumour recurrence, the patient was qualified to non-standard chemotherapy (erlotinib).

The patient remains under constant clinical care.

Discussion

In the above-described patient, the coexistence of tuberculosis in the course of non-small cell lung cancer with metastases to the eyeballs was stated. The literature data claims that the frequency of lung cancer is higher in patients with an active form of tuberculosis. A shorter lifespan of patients with lung cancer, in whom the specific process had been diagnosed previously to neoplasm was also proven. The analysis by Yu and Lang elicited that subjects with tuberculosis were eleven times more exposed to lung cancer development than patients without this mor-

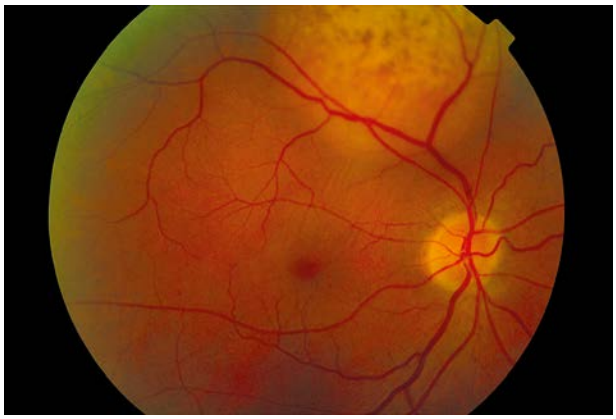

Fig. 1. 15.07.2010 – right eye fundus: amelanotic tumor of right eyeball's choroid coat in eyeball's posterior pole

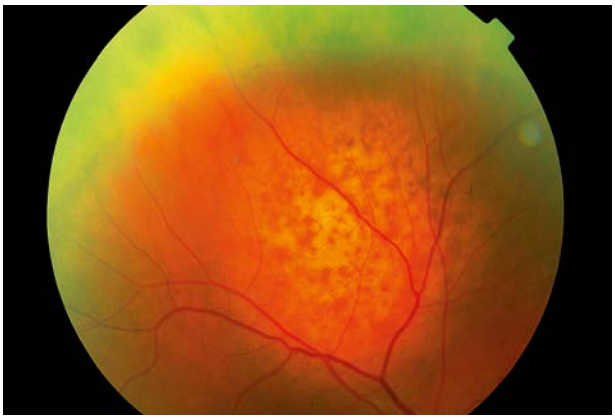

Fig. 2. 15.09.2010 – right eye fundus: bright, flat area of retinal epithelium reshuffle, related to right eyeball's tumor disappearance

bidity were. The mortality was higher as well (eight times) among those suffering from tuberculosis [1, 2].

Vento and Lanzafame emphasise in their research that the relationship between these two morbidities must eventually be confirmed. Therefore, it should be established which disease develops first. As yet, scientists have not been able to unambiguously answer this question. There are studies which suggest that tuberculosis might support lung cancer development by evoking inflammation and fibrosis with subsequent lung neoplasia. Adversely, other studies claim that lung cancer is a risk factor of tuberculosis, presumably by decreasing immunity and thereby elevating the risk of new infection development or reactivation of an old one [3].

How does tuberculosis increase the risk of lung cancer incidence? It was proven that the inflammation process and fibrosis are essential, although many mediators of inflammation, including a tumour necrosis factor α (TNF-α), play a significant role in *Mycobacterium tuberculosis* infection control [4]. Tumour necrosis factor α might prolong tumour cell lifetime by influencing the induction of genes encoding nuclear factor κB – dependent on TNF-α antiapoptotic molecules. Moreover, tumour necrosis factor contributes to neoplasia by impairing vessel permeability and inducing production of genotoxic particles, such as nitric monoxide, which evokes DNA damage and mutation of lung tissue epithelial cells [5]. Nowadays, repairing processes in a phthisic tissue are characterised by high fibroblast synthesis, and thereby lead to fibrosis and neoplastic tissue development in a phthisically altered area [6].

The crucial factors in tuberculosis development are respiratory and digestive system neoplasms (especially neoplasm of the oral cavity, nasopharyngeal cavity, oesophagus and lungs) as well as the haematopoietic system (mainly Hodgkin's and non-Hodgkin's lymphomas and leukemias) [7]. Close attention should be paid to the role of applied chemotherapy, which contributes to immunity decrease and elevates the risk of *Mycobacterium tuberculosis complex* infection [3, 6].

The complicated relation between tuberculosis and neoplasm causes problems in accurate diagnosis of prior morbidity, especially in countries with a high coefficient of tuberculosis incidence [1]. There are four aspects to deliberate.

Firstly, malignant neoplasm should be suspected in every case when typical clinical symptoms or any abnormalities in imaging examinations (chest X-ray and CT) suggesting neoplastic process are present in patients previously infected with Mycobacterium tuberculosis [7].

Secondly, the diagnosis of active tuberculosis should be pursued in subjects with neoplasm diagnosed during applied chemoprophylaxis. In such cases the QuantiFERON-TB Gold test in blood serum is indicated [8, 9].

Thirdly, tuberculosis simulates some of the clinical and radiological features of lung cancer, thereby causing diagnostic difficulties and contributing to a delay in proper diagnosis establishment. However, it is clear that meticulous risk assessment of the tuberculosis incidence in patients suffering from lung cancer should be carried out [10, 11].

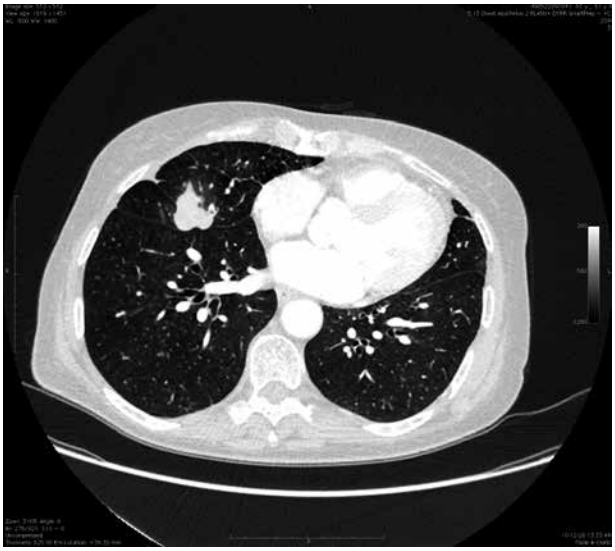

Fig. 3. 20.12.2010 – chest CT: in IV segment of right lung visible tumor 33 mm × 17 mm

And finally, Sheti and Engels, in their study, announced that for the elevation of lung cancer, the incidence the HIV infection, which undoubtedly is largely coincidental with *Mycobacterium tuberculosis* infection, is responsible [12].

In conclusion:

1. The coexistence of tuberculosis in patients with diagnosed non-small cell lung cancer during applied chemotherapy raises a number of diagnostic problems and may impair the effectiveness of applied cytostatic treatment.
2. Metastases to the eyeballs in non-small cell lung cancer are a very rare phenomenon, which worsens prognosis in the initial stage of diagnosis and treatment of neoplastic process. (Shields *et al*. stated that the mean lifetime of patients with eyeball metastases ranges from 2 to 2.5 years, with a maximum of 13 years [13]).
3. Lung cancer is a risk factor of tuberculosis development by causing immunity decrease.
4. Chemotherapy, as one of the methods of neoplasm treatment, increases the risk of development of *Mycobacterium tuberculosis complex* infection.

Authors declare no conflict of interest.

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