

CLINICAL CASE OF SYSTEMIC SCLEROSIS IN THE COURSE OF LUNG ADENOCARCINOMA

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Abstract. We present a patient with a 5-year systemic sclerosis with diffuse skin manifestations, capillaroscopic data to confirm diagnosis, elevated levels of ANA-antibodies, Anti-Sox-1, Anti-Ro-52 and Anti-Histone in the course of lung adenocarcinoma (proven by fibrobronchoscopy and biopsy) and brain metastasis in consequence. From the clinical examination, it is established diffuse skin manifestations, weakened vesicular respiration in right site of lung, astheno-adynamic syndrome, shortness of breath with usual physical exertion. From lung function tests, FVC is 58% and FEV1 is 59%. The adenocarcinoma is located on a wide area in the right half of the lung and not indicated for surgical treatment. The patient completed 4 courses of chemotherapy with Alimta + Cisplatin from March 2016 to July 2016, 7 courses of Docetaxel from February 2017 to September 2017, and radiotherapy. One year later complaints of forgetting of words, difficult reading and writing appeared. Computed tomography (CT) shows intracranial tumor formation with heterogeneous structure in left frontal brain half – metastasis after lung adenocarcinoma. Operative removal of tumor formation and postoperative radiotherapy took place and Depakine Chrono 2 times 500 mg daily was prescribed. The treatment for systemic sclerosis was followed by 8 mg Methylprednisolone and 250 mg Cuprenil with good therapeutic effect.

Key words: systemic sclerosis (scleroderma), lung cancer, paraneoplastic syndrome

INTRODUCTION

We present a patient with a 5-year systemic sclerosis with diffuse skin manifestations, capillaroscopic data confirming diagnosis, elevated levels of ANA-antibodies, Anti-Sox-1, Anti-Ro-52 and Anti-Histone, in the course of lung adenocarcinoma (proven by fibrobronchoscopy and biopsy) and brain metastasis in consequence.

The patient reported whitening and bruising on the fingers of hands, irritating dry cough, periodically with blood, thirst, and easily occurring chronic fatigue. From the clinical examination, it is established diffuse skin manifestations, weakened vesicular respiration in right site of lung, astheno-adynamic syndrome, shortness of breath with usual physical exertion.

Capillaroscopy performed in February 2016 established reduced number of capillaries, multitude of gigantic capillaries with hemorrhages, pericapillary edema, and aneurismal extensions. The study showed capillaroscopic data for SSC II degree. The results from immunological research shows elevated levels of ANA-screening antibodies 1:1280 ME – the normal is 1:80 ME, Anti-Ro-52 – 22 ME – the normal is up to 5 ME, and Anti-Histone – 8 ME – the normal is up to 5 ME, Anti-Sox-1 – 6 ME – the normal is up to 5 ME (Fig. 1).

From lung function tests, FVC is 58% and FEV1 is 59%. Fibrobronchoscopy with biopsy were performed and lung adenocarcinoma was proven. The adeno-

carcinoma is located on a wide area in the right half of the lung and not indicated for surgical treatment

The patient completed 4 courses of chemotherapy with Alimta + Cisplatin from March 2016 to July 2016. Follow-up computed tomography (CT) scan took place. No data for reduction of volume of carcinoma was found. In the right lung – upper lobe and sixth segment of lower part, a dense zone of consolidation of parenchyma, condensed dilated and deformed bronchi, and multiple dilated vessels were found (Fig. 2).

7 courses of Docetaxel were prescribed from February 2017 to September 2017, and radiotherapy took place (Fig. 3). Follow-up CT scan showed reduction of volume of carcinoma.

One year later complaints of forgetting of words, difficult reading and writing appeared. Computed tomography (CT) scan showed intracranial tumor formation with heterogeneous structure in left frontal brain half – metastasis after lung adenocarcinoma, presence of solid and cystic components with axial dimensions 30/24 mm (Fig. 4). Follow-up CT scan of lung showed data for stabilization of volume of carcinoma (Fig. 5).

Operative removal of tumor formation and postoperative radiotherapy took place and Depakine Chrono 2 times 500 mg daily was prescribed. The treatment for systemic sclerosis was followed by 8 mg Methylprednisolone and 250 mg Cuprenil with good therapeutic effect.



Fig. 1. Computed tomography image of lung of 12/07/2016

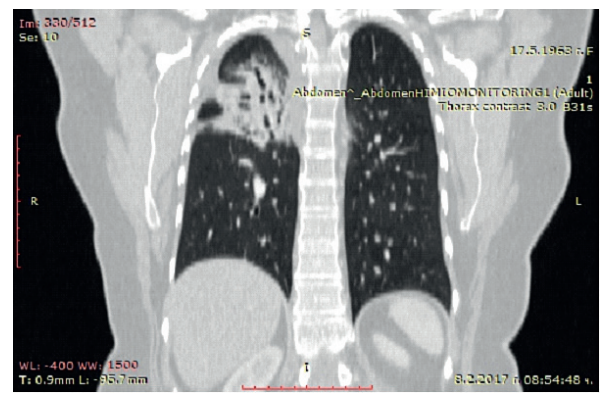


Fig. 2. Computed tomography image of lung of 08/02/2017



Fig. 3. Computed tomography image of lung of 06/10/2017

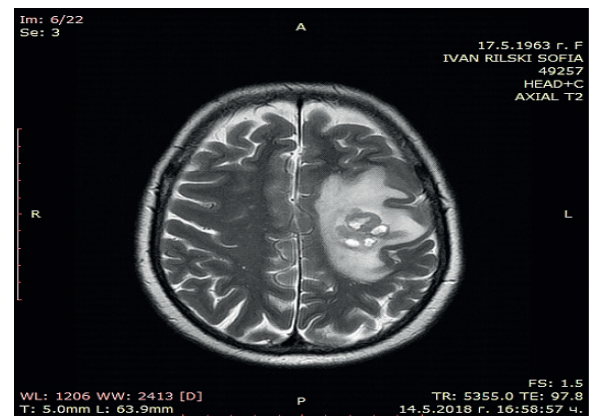


Fig. 4. Computed tomography image of brain of 14/05/2018

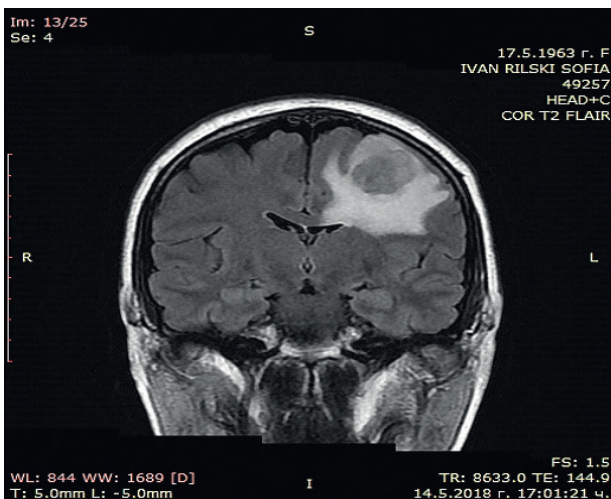


Fig. 5. Computed tomography image of lung of 30/08/2018

DISCUSSION

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder, characterized by multi-system involvement, vasculopathy and fibrosis [1]. Similar to the general population, an increase in the

incidence of malignant tumors has also been noted in the last decades. Together with a better management of scleroderma-related complications due to medical progress in SSc, cancer has thus become a leading cause of mortality in this disease, resulting in about 11% of deaths (third cause) according to the study on death certificates EUSTAR database [2].

Common mechanisms and pathways may be involved both in fibrogenesis and oncogenesis, and recent data have suggested that autoimmunity in SSc may be triggered by antigen mutation in tumor cells [3, 4, 5].

The association of lung cancer and SSc is widely documented in the literature with a SIR ranging from 4.2 to 5.9 [6, 7, 8]. In a retrospective Italian study of 318 patients, 16 patients had lung cancer (5%) [9].

Our clinical case is a patient with systemic sclerosis, connected with lung adenocarcinoma.

Several scleroderma-like syndromes have been described after anti-mitotic treatment. Docetaxel, a molecule used in the therapeutic arsenal of many cancers, is known to have skin toxicity, with possible scleroderma-like lesions. The mechanisms leading

to docetaxel cutaneous fibrosis are not fully understood. Some authors suggest that the deposition of an extracellular matrix glycoprotein (i.e., versican) after docetaxel or paclitaxel treatment may play a role in the pathogenesis of docetaxel-induced scleroderma [10]. Recently, the first case of scleroderma secondary to docetaxel with organ involvement (PAH and renal scleroderma crisis) has been published [11]. One of the explanations would be the possibility of endothelial cell damage induced by oxidative stress secondary to docetaxel [12].

The patient that we present was treated with docetaxel after debut of SSC, connected with lung adenocarcinoma. It is not clear whether the treatment with this medication contributed for progression of skin lesions.

More recently, anticancer immunotherapy has been shown to trigger autoimmunity, and a few cases of scleroderma have been reported in the literature. In this context, the complexity of the interplay between anti-cancer preexisting autoimmunity, genuine paraneoplastic syndromes and the effects of immune system stimulation by biologics is striking, and strengthens the relationships between SSC and malignancy.

The exact definition of a paraneoplastic syndrome may vary greatly among authors and remains debatable. First, one prerequisite for paraneoplastic phenomenon lies in this "temporal clustering," viz. a short interval between the onset of cancer and the onset of autoimmune disease. Of note, cancer could precede SSC onset, and vice-versa. This "short" interval is however vague, but 3 to 5 years before and after SSC diagnosis could be acceptable since it corresponds to a "peak" of frequency in cancer diagnosis in previous studies. Second, there should be a parallel evolution between cancer and autoimmunity, with autoimmune flares accompanying cancer relapses. Conversely, cancer resection should lead to the remission of the associated autoimmune condition. However, such a theoretical conception of paraneoplastic phenomena may be far away from the reality observed concerning SSC, where no resolution of autoimmunity has been described after cancer healing [13].

Our clinical case shows in parallel development of lung adenocarcinoma and SSC. Probably, the early one carcinoma has resulted in activation of autoimmune reaction and clinical manifestations of SSC.

Conceptually, autoimmunity may be associated with oncogenesis and anti-tumor defense. This is also consistent with the observation of cancer developing sometime after autoimmunity, since autoimmune response in this context may be triggered in the very early stages of cancer development, even

in premalignant disease. For instance, autoantibody production has been shown to appear years before cancer diagnosis in such context [13].

Interestingly, specific anti-tumor activity of antinuclear antibody (ANA) via antibody-dependent cell-mediated cytotoxicity (ADCC) has been described [14].

Beyond simple epidemiological observations, intriguing and complex bilateral relationships exist between SSC and malignancy, supported by a growing body of data involving the immune system and other contributors such as genetic and epigenetic changes, environmental factors, including oxidative stress.

In our clinical case elevated levels of Anti-Sox-1-antibodies were established. The presence of Anti-Sox-1 (AGNA) is connected with paraneoplastic neuropathies and can serve for differential diagnosis with other autoimmune neuropathies. The most common form is connected with small cell lung carcinoma, but communicated other form of lung carcinoma.

The presence of Anti-Ro-52 и Anti-Histone is connected with interaction between carcinoma and autoimmunity resulting in development of autoimmune disease. The review of the scientific literature represents single clinical cases. Combined treatment for autoimmune and malignant disease is important for clinical improvement of these patients.

Deciphering the mechanisms of autoimmunity through the prism of cancer immunosurveillance is even more fascinating in the era of anticancer immunotherapy, and will undoubtedly lead to new breakthroughs both in the field of autoimmunity and cancer.

The author declares that he does not conflict of interest related to the publication.

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