Coexistence of rheumatic and neoplastic diseases may take different forms. Rheumatic paraneoplastic syndromes, including systemic sclerosis, scleroderma-like changes and Raynaud’s phenomenon are induced by substances secreted by neoplastic cells and immunological disturbances connected with malignancy. They may precede the clinical manifestation of neoplasm, occur simultaneously or after its diagnosis. In turn, chronic course of rheumatic diseases (Sjögren’s syndrome, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis) by immunologic stimulation may promote carcinogenesis. Genetic, environmental factors (viruses, chemical substances, radiation) and alterations of immunological surveillance may be the cause of both rheumatic and paraneoplastic disorders. Anticancer therapy may cause rheumatic diseases and immunosuppressive agents used in patients with rheumatic syndromes may have carcinogenic effect. Patients with long-standing or atypical course of rheumatic disorders, positive family or personal history of neoplastic disease, positive cancer markers, monoclonal antibodies or presence of other paraneoplastic syndromes should be diagnosed as possibly having occult neoplasm. In this paper we reviewed available literature on coexistence of rheumatic processes and malignancies to attract particular attention to practical aspects of this vital issue.

**Key words:** neoplasm, scleroderma-like syndrome, systemic sclerosis
Rheumatic paraneoplastic syndromes

Rheumatic paraneoplastic syndromes occurring during the course of the neoplastic disease may precede its diagnosis by a couple of years, appear simultaneously with clinical manifestation of the malignancy or develop after some time from diagnosing the neoplasm. It is often difficult to differentiate them from the idiopathic form. It is believed that the presence of such changes predicts poor outcomes of the malignancy [7-10]. Along with the recovery from the neoplasm the rheumatic lesions subside, and their reappearance may suggest relapse of the disease [15,16].

Rheumatic paraneoplastic syndromes are induced by a number of factors such as hormones, cytokines, peptides, autocrine and paracrine mediators excreted by the tumor [17,18]. Since the neoplastic cells do not undergo apoptosis, they may be a source of autoantigens, inducing the dysfunction of the immune surveillance, which stimulates the production of autoantibodies or cytotoxic lymphocytes. The circulating autoantibodies, immune complexes or sensitized T lymphocytes, together with the mediators excreted by the neoplasm, may damage the endothelial cells or the mesenchymal tissue [19,20]. The iatrogenic factors associated with anticancer treatment, including some drugs or ionizing radiation, may also lead to the rheumatic lesions [21-27].

Neoplasia in the course of rheumatic disorders

An example of persistent disorders of immune regulation in the course of rheumatic diseases, which may initiate a neoplastic process, is Sjögren’s syndrome, associated with a 44- fold increase in the risk of developing non-Hodgkin lymphoma [28,29]. In genetically predisposed individuals with Sjögren’s syndrome (with the presence of HLA [histocompatibility antigens] B8, DR2, DR3, DQ) the environmental factors (viral infection, Epstein-Barr virus, cytomegalovirus, hepatitis C virus, retroviruses or UV radiation) alter the immune system. The alterations consist in T lymphocytes CD4+ infiltration, to a lesser degree in T lymphocytes CD8+ and B lymphocytes, plasmocytes, macrophages and mastocytes infiltrations in the salivary glands, lacrimal glands as well as in other organs and tissues. There are produced autoantibodies (among others the Ro, La antibodies, and antibodies against the M3 muscarinic receptor), several cytokines, including interferon γ (INF-γ). In some cases B cell monoclonal proliferation has been observed, which may lead to the development of lymphomas. A similar sequence of events has been reported in rheumatoid arthritis, polymyositis, dermatomyositis, systemic lupus erythematosus and SSc [14,30-34].

In contrast to paraneoplastic rheumatic syndromes, the time between the onset of the rheumatic disorder and the first manifestation of the neoplastic disease is substantially longer and may amount even to 20 years [11]. The use of potent immunosuppressants like methotrexate [35], cyclophosphamide [36] and cyclosporine [37] in the therapy of severe rheumatic lesions increases the risk of cancer (Tab.).

Ethiopathogenesis of SSc and scleroderma-like syndromes

Systemic sclerosis and scleroderma-like syndromes are characterized by complex immune disorders, vascular damage and overproduction of the extracellular matrix by activated fibroblasts. The development of these diseases is associated with complex interactions between the endothelial cells, lymphocytes, macrophages, fibroblasts as well as with the action of a number of mediators, including cytokines, chemokines and growth factors – excreted by the inflammatory and mesenchymal cells, which play an important part in the development of fibrosis [38]. The immunologic reactions involved in the pathogenesis of SSc are claimed to promote also the development of malignancy [39]. High concentrations of the profibrotic cytokines participating in the pathogenesis of SSc, like transforming growth factor β (TGF-β), are found in some cancers (for example, cancer of the breast, ovary, kidney) [40].

Both SSc and scleroderma-like syndromes may be triggered by various factors, including tryptophan [41], silica dust, aromatic hydrocarbons, aliphatic solvents, chlorinated hydrocarbons, vinyl chloride, trichloroethylene, epoxide resins, carboplas, pentazocine, cocaine, fenfluramine, D-penicillamine. Some of the substances, i.e. organic solvents, may be contemporaneously a risk factor of neoplastic disease as well as SSc [21]. In particular, the silicon breast implants play an important part. It has been demonstrated that in population of women with silicon breast implants the relative risk of SSc is increased [42]. There are also reports regarding abnormal esophageal motility similar to that observed in SSc (nearly absent peristalsis in the distal two thirds of the esophagus and decreased lower sphincter pressure) in breast-fed children of mothers with silicone implants [43].

Association between SSc and neoplastic diseases

The association between the neoplasm and SSc complicated with lung fibrosis was described for the first time in 1953 [44]. The frequency of cancer in patients with SSc is estimated to be 3–7% [34], and in some of the studies even up to 11.4% [45]. The standardized incidence ratio for all cancers among these patients is 2.1 times higher, and for lung cancer 7.4–16.5 higher than in the general population [2]. The standardized incidence ratio for hematopoietic cancers amounted to 2.3, of primary liver cancer to 3.3 and of nonmelanoma skin cancers to 3.3 [3].

The most common malignancies associated with SSc include lung and breast cancer and subsequently neoplasm of the hematopoietic and lymphatic system. Older age at diagnosis of SSc is recognized as a significant risk factor of neoplasia [46]. The relationship between the duration of scleroderma and the type of carcinoma has been described [47]. Systemic sclerosis in its early phase is associated with the development of breast cancer, and after a decade with lung cancer. Interestingly, the
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<td>Neoplasm of the lung, breast, hematopoietic and lymphatic (acute and chronic granulocytic leukemia, Waldenström’s macroglobulinaemia, Burkitt lymphoma and immunocytic lymphoma)</td>
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ACA – anticentromere antibodies, DM/PM – dermatomyositis/polymyositis, POEMS syndrome – polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes
neoplasm which is most common in patients with SSc – lung cancer, seems to be not associated with cigarette smoking [48], and the most frequent type of carcinoma is small cell carcinoma [49].

Bielfeld described 21 cases of neoplastic lesions in patients with SSc – in 8 patients the malignancy preceded SSc by 3 to 24 years, in five cases both of the diseases were diagnosed in the same year. In 8 patients SSc manifested 5 to 20 years before the neoplasm. In case of Burkitt lymphoma the chemotherapy which led to remission alleviated the symptoms of SSc, whereas the drastic crisis in patients with chronic myelogenous leukemia aggravated the symptoms of scleroderma [50].

There are reports showing coexistence of SSc with acute and chronic myelogenous leukemia, Waldenstrom's macroglobulinemia, Burkitt lymphoma as well as immunocytic lymphoma [45,50,51]. A study conducted in Australia demonstrated that the risk of cancer (especially lung cancer) is increased in patients with scleroderma as compared with the general population. There were no differences between patients with limited (lSSc) and diffuse scleroderma (dSSc) and there was no association between the incidence of cancer and the presence of antici-

tromere antibodies (ACA) or anti-topoisomerase I antibodies (anti-SCI-70). It has been demonstrated that in the majority of cases SSc manifested after the disclosure of breast carcinoma, whereas in case of lung carcinoma scleroderma preceded the diagnosis of malignancy [46]. Pearson et al. [2] reported that lung cancer was 16.5 times more prevalent in patients with lSSc with the presence of anticentromere antibodies (ACA), whereas lung fibrosis was present in 62% of the patients with SSc, who developed lung cancer, in comparison to 28% of the patients with SSc who remained cancer-free. It has been postulated that lung carcinoma is more frequent in patients with pulmonary fibrosis.

The results of the study by Higuchi [52] demonstrated that the presence of ACA significantly increased the risk of cancer in the SSc patients, while the erythrocyte sedimentation rate, serum lactate dehydrogenase concentration, serum gamma-globulin concentration, the presence of antinuclear antibody as well as of anti-topoisomerase I antibody were not associated with cancer in SSc. Therefore, the patients positive for ACA should be monitored for neoplastic changes. On the other hand, the results reported by French investigators [45] contradicted these observations because they found no association between the frequency of neoplastic lesions and the sex, type of SSc, pulmonary fibrosis, Sjögren's syndrome, antinuclear antibodies and anti-SCI-70 titer, as well as immunosuppressant therapy. Similarly, the study by Derk et al. [53] reports no differences in autoantibody patterns among SSc patients with and without a neoplasm.

It has been suggested that anti-SCI-70 antibodies present in 10–15% of patients with SSc, directed against topoisomerase I, which is involved in DNA repair, may disturb the reparation of damaged genome, whereas ACA found in 80% of patients with lSSc may lead to chromosome damage. In both cases the risk of neoplastic transformation increases. On the other hand, E-selectin overexpression observed in SSc [54], which influences the endothelial cells, may facilitate cancer invasion by stimulation of the angiogenesis. Moreover, the neoplastic cells may express E-selectin ligand and adhere to endothelial cells, facilitating tumor metastasis, therefore SSc may promote the spreading of neoplasm [55].

Pseudoscleroderma, as a paraneoplastic symptom, may be triggered by substances produced by neoplasm. An overexpression of connective tissue growth factor and collagen type I has been observed in patients with lung cancer [56]. Scleroderma-like skin lesions have been reported in patients with cancer of the stomach, breast, lungs, nasopharynx, together with with melanoma and sarcoma [1,7,8,57-63].

Scleroderma-like syndromes may be found in patients with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes), associated with a extremely rare type of plasmocytoma presenting as localized osteosclerotic lesion. The symptoms of POEMS syndrome include also chronic sensorimotor polyneuropathy, organomegaly (hepatosplenomegaly) and lymphadenopathy, endocrinopathy in the form of hypogonadism, gynecomastia, adrenocortical insufficiency, hypothyroidism, diabetes mellitus, hyperparathyroidism; a characteristic feature is also the presence of monoclonal protein [64]. It has been suggested that the scleroderma-like skin lesions may result from the imbalance between cytokines with elevated levels of proinflammatory factors like interleukin-1, interleukin-6 and tumor necrosis factor α.

Scleroderma-like lesions and calcifications of the subcutaneous tissue are also present in Werner's syndrome [65]. Werner's syndrome is a very rare autosomal recessive disorder associated with premature aging which becomes apparent around puberty. The disorder is caused by a defect of the WRN gene that is located on the short arm of the 8th chromosome and codes DNA helicase, which disturbs the separation of double-strand DNA and subsequently leads to incorrect replication and repair. The symptoms of Werner's syndrome are short stature, loss and graying of hair, cataract, hypogonadism, premature atherosclerosis, heart diseases, diabetes mellitus, osteoporosis. The characteristic feature is genomic instability, resulting in increased probability of somatic mutations and a higher frequency of neoplastic lesions, especially mesenchymal tumors, including sarcomas and meningiomas [66].

It is claimed that genetic instability may result in neoplastic diseases and SSc. Furthermore, in patients with SSc IgG anti-WRN helicase antibody is present, as compared with the control group, and their titers correlated with the levels of anti-topoisomerase I antibody in the same blood samples and were significantly higher in diffuse SSc than in the limited type of the disease [67].

Patients with SSc may have damaged genome (higher proportion of chromosome breakage, deletions of the centric fragments, spontaneous nucleotide repetitions, chromosome fragility, additionally damaged by the immunosuppressants) which
promotes carcinogenesis [68]. The study cited above presents preliminary data of acquired genetic defects in scleroderma – the investigators determined the prevalence of somatic mutations at the glycoporphin-A (GPA) locus and loss of expression of one of the GPA alleles in patients with diffuse and limited cutaneous scleroderma (dSSc/lSSc). Patients with scleroderma had a higher prevalence of mean total somatic mutation as compared with the control group. Patients with dSSc had more frequent the mean somatic mutation as compared with lSSc. Patients with scleroderma presented a higher proportion of mitotic recombinant mutations than that of inactivating mutations. There was no correlation between the frequency of somatic mutation and disease duration, age at onset or autoantibody status. It was demonstrated that the risk of cancer is higher in first-degree relatives of patients with SSc, which suggests that a common genetic and environmental factor may be involved in the development of both cancer and SSc. The risk in the study group amounted to 27.7%, compared to 9% in the control group [69].

Raynaud’s phenomenon in the course of neoplastic diseases

Raynaud’s phenomenon may be a first symptom of SSc, sometimes preceding the skin and organ changes by many years. The presence of Raynaud’s phenomenon in patients above 50 years of life, especially with asymmetric involvement of the fingers or progressive necrosis, may be a paraneoplastic symptom, preceding the disclosure of the neoplasm [70]. There are reports of disappearance of Raynaud’s phenomenon after tumorectomy [71].

The occurrence of Raynaud’s phenomenon may be associated with neoplasm of the lungs, ovary, small intestine, breast, pancreas, kidney, lymphoma, plasmocytoma or leukemia [1,9,57,70]. A paraneoplastic Raynaud’s phenomenon was also described in patients with Kaposi’s sarcoma treated with vincristine and bleomycin [72]. The etiology of Raynaud’s phenomenon in neoplastic diseases in unknown, it may be caused by paraproteins, cryoglobulins and certain cytokines. It is often resistant to vasodilators and sympathectomy, and may lead to digital necrosis even in 80% of the patients [70].

The role of pharmacotherapy and other forms of treatment on the development of SSc and neoplastic changes

It is believed that the immunosuppressants used in SSc may trigger neoplasia [47]. It applies especially to the most powerful carcinogenic drug – cyclophosphamide, which induce lymphoreticular neoplasia and carcinoma of the urinary bladder.

On the other hand, the preparations used in the treatment of neoplastic diseases may trigger scleroderma-like syndromes, associated probably with excessive local accumulation of drugs/metabolites in the subcutaneous tissue [73]. This phenomenon concerns docetaxel [22] paclitaxel [23], bleomycin [24], carboplatine [25], gemcitabine [26], uracyl-tegafur [74]. In case of the last two substances the changes were reversible and disappeared within several months from discontinuation of the treatment.

The arguments, which indicate a direct correlation between skin lesions and the effect of the drug are: rapid appearance of the lesions after introducing the treatment, quick regression of the fibrotic changes (at least partial) after discontinuation of the drug. A precise pathophysiological mechanism is not known, probably the drugs/metabolites are excessively accumulated locally in the subcutaneous tissue. Additionally, the primary SSc exclusion is based on no involvement of the internal organs and the absence of autoantibodies (ACA, anti-ScI-70). An experimental animal model consists in evoking SSc symptoms in mice after local injection of bleomycin [75], which generates DNA lesions causing apoptosis induction and expression of p53, p21 as well as of proliferating cell nuclear antigen (PCNA) in the skin damaged by bleomycin administration. The study showed that the apoptotic cells appeared after 1 week and the expression of p53, p21 and PCNA (mainly in the mesenchymal tissue) increased after 1–2 weeks from the injection of bleomycin [76].

Other methods used in the treatment of cancer patients, like radiotherapy, may be also associated with scleroderma-like lesions [26,77].

Another issue represent scleroderma-like lesions resulting from graft versus host disease, in transplant patients, especially after bone marrow transplantation in the treatment of myeloproliferative syndromes. They are triggered by the imbalance between autoregulatory and autoreactive lymphocytes, as well as the phenomenon of microchimerism, that is the presence of a small amount of circulating cells transferred from another individual [78]. It is believed that the phenomenon of microchimerism, especially maternal-fetal (the presence of maternal cells in the fetus), plays an important role in the pathogenesis of SSc [79].

High concentrations of the profibrotic cytokines associated with the pathogenesis of SSc, like TGF-β, are found in some cancers (breast, ovarian, renal) [1]. It is disputable if these immunological abnormalities may increase the incidence of malignant tumors linked with dSSc. Some authors think that this factor is crucial to promotion of fibrosis and uncontrolled fibroblast proliferation [80].

SUMMARY

Systemic sclerosis and neoplastic disorders may coexist one with the other. A crucial role may have some environmental factors, like for example hypertryptophanemia or organic solvents, which may lead to both carcinogenesis and scleroderma-like changes. Furthermore, DNA repair defects, like in Werner’s syndrome, where scleroderma-like changes coexist with
neoplasms, may be a reason of multiple somatic mutations leading to malignancy and autoimmunization. Immunological disorders associated with neoplasia may cause scleroderma-like lesions, as well as chronic autoimmunization may trigger carcinogenesis. Several cytostatic drugs have been reported to induce malignant and scleroderma-like lesions.

In many cases it is necessary to differentiate whether SSc is idiopathic or if it is a paraneoplastic symptom. The features that suggest paraneoplastic syndrome are a history of neoplasia (also family history), exposition to carcinogens, onset beginning of the symptoms in elderly, serious general symptoms (fever, asthenia, weight loss), a close temporal association between the paraneoplastic symptoms and the diagnosis of cancer, a weak response to the conventional treatment, improvement of the symptoms after antineoplastic treatment, recurrence of symptoms after antineoplastic treatment, symptoms after antineoplastic treatment, recurrence of symptoms after antineoplastic treatment.

The primary SSc is excluded when the skin manifestations are not associated with internal organ involvement and there are no autoantibodies (ACA, anti-SC1-70).

The connection between the rheumatic diseases, including systemic scleroderma, and the occurrence of neoplasms suggests an increased oncological vigilance, especially in case of a positive history of neoplastic changes, an atypical course of the rheumatic disorder, the presence of other paraneoplastic symptoms, serological markers of the neoplasm or monoclonal antibodies. Unless the rheumatic disorders are associated with the above mentioned symptoms, which directly indicate the neoplastic disease, intensive diagnostic evaluation of the malignancy is not recommended.

REFERENCES