

Cancer and rheumatic diseases. Methodological and clinical pitfalls in searching links between these diseases

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Results of studies on coexistence of rheumatic and oncological diseases are somewhat conflicting in the literature. This is probably due to various methodological problems of the conducted research such as: small groups of patients, possible Berkson's bias, lack of information about the most important factors affecting the risk of developing cancer including lifestyle, body mass index, use of tobacco and alcohol, family history of cancer and autoimmune diseases, misclassification of diseases in administrative registries, differences including geographical, racial factors, and a relatively short observation period. The risk of cancer development or recurrence in patients treated for rheumatic disease is very low, estimated as 2–5 cases per 1000 patients treated annually, and even lower in patients with cured cancer and 5 years after completion of oncological treatment. In the absence of clear recommendations for cancer screening of patients with rheumatic diseases, there is a need to develop guidelines for screening.

Key words: cancer, rheumatologic diseases, screening, coexisting diseases and malignancies, multi-disease phenomenon

Introduction

The literature data on the relationship between rheumatic diseases and malignancies dates back to the second decade of the 20th century, when Stertz described a case in 1916 of a patient with inflammatory muscle disease and coexisting gastric cancer [1]. Cancer and rheumatic diseases have similar etiological factors, which generally boil down to the lack of or impaired immune surveillance of the body. The main cause of cancer development in patients with rheumatic diseases is a chronic activation of the immune system and inflammatory process, which may be explained to some extent by common etiopathological factors in both groups of diseases: genetic,

environmental, immune surveillance disorders, which is referred to as multi-disease phenomenon.

Methodological pitfalls

The results of studies on coexistence of rheumatic and oncological diseases are somewhat conflicting in the literature [2, 3]. This is probably due to various methodological problems of the conducted research. Most analyses of the association between rheumatic diseases and cancer are based on small groups of patients, which, from a statistical point of view, make it difficult to see possible associations. Moreover, in analyses of hospital registries of oncological patients or patients with rheumatic di-

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seases, Berkson's bias may appear when paradoxically, there are more patients with rheumatic and cancer diseases than with rheumatic diseases alone. This happens when control groups are not included. What is more, the literature reports generally do not provide information about the most important factors affecting the risk of developing cancer including lifestyle, body mass index, use of tobacco and alcohol, family history of cancer and autoimmune diseases. In addition, based on available data from administrative registries, there is a possibility of misclassification of diseases with respect to both rheumatic and cancer diseases, which in turn may lead to misinterpretation of data on cancer risk. Also, associations between rheumatic diseases and cancer vary by type of disease, population and geographic zones, racial and ethnic factors. For example, a study performed in one geographical area is not corroborated by a study performed in another part of the world. Meta-analyses concerning cancer development in the course of biological therapy of rheumatic diseases, and likewise, are burdened with methodological errors such as a relatively short observation period compared to known and long-used cytostatic drugs, basing the assessment of treatment effectiveness on time to disease progression instead of overall survival time. Another problem is survival bias resulting from the fact that rapidly progressive malignancies may be underrepresented because patients may die prematurely or die from other (noncancerous) causes before cancer diagnosis [4].

Many studies use short follow-up periods making long-term cancer risk analysis difficult. Studies on the association of drugs used in rheumatology in the induction of secondary cancers are often based on data from transplantation. However, the use of observations from transplantation has its limitations, as multiple drugs are used in immunosuppressive therapy after transplantation and it is difficult to determine which (if any) drug is responsible for tumor development or recurrence. Moreover, it is difficult to translate data from immunosuppression used in transplantology to immunosuppression used in rheumatology, because in the first case there is no autoimmune disease, and in rheumatic diseases autoimmune processes are usually present. Some authors raise the problem that data obtained from randomized clinical studies and meta-analyses do not always meet the needs of patients and clinicians due to potential biases favoring positive results of these studies and a paucity of head-to-head comparisons between biologically active agents [5].

Coexistence of rheumatic diseases and cancer

Taking into account all the above mentioned methodological limitations, many publications point to the coexistence of rheumatic diseases and cancer, which can take the form of paraneoplastic syndromes, cancers induced by rheumatic disease therapy and conversely rheumatic disease induced by anticancer therapy [6–8]. Some rheumatic diseases may increase the incidence of cancer and a problem of particular

importance is the induction of cancer under the influence of antirheumatic therapy. The extent of this problem is impossible to assess due to the lack of complete knowledge about the etiopathogenesis of both groups of the diseases and the inability to distinguish secondary from primary metachronous tumors.

Basically, the risk of cancer development or recurrence in patients treated for rheumatic disease is very low, estimated as 2–5 cases per 1000 patients treated annually, and even lower in patients with cured cancer and 5 years after completion of oncological treatment [9].

A study by Chang et al. evaluating cancer incidence in patients with different rheumatic diseases showed that different rheumatic diseases are associated with the risk of specific cancers [3]. According to Penn, the risk of cancer recurrence after rheumatic disease therapy can be defined as:

- low (0–10%) and concerning cancers of: testicle, cervix, thyroid and lymphoma,
- medium (11–25%) and concerning cancers of the endometrium, colon, prostate, breast, Wilms tumor,
- high (above 25%) and it involves bladder cancer, kidney, skin, malignant melanoma, sarcomas and multiple myeloma [10].

The mutual association between cancer and rheumatic diseases is best known in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), inflammatory myopathies, scleroderma and vasculitis. The highest association was described in lymphomas, but the association of rheumatic diseases with solid tumours has been inconsistent. In the epidemiological study based on the National Health and Nutrition Examination Survey (NHANES), breast and prostate cancer were the most common malignancies observed in patients with rheumatoid arthritis [11]. Meta-analysis of Simon et al. showed increased risk in RA patients for lymphomas, and to a lower degree for lung cancer but not for other malignancies [12]. These results are consistent with reports from other publications [13–14]. RA conveys some risk for cancer development but also influences cancer survival in patients with concomitant RA, especially in elderly patients with breast and prostate cancer [15]. In a retrospective cohort study, higher mortality was also found in RA patients with lung cancer [16]. Giat et al. showed that biologic therapy in RA does not significantly increase the risk of malignancy in RA patients, but this is influenced by different ethnic and environmental factors [17]. RA and dermatomyositis and polymyositis is associated with higher mortality in patients with lung and breast cancer, whereas systemic sclerosis is associated with decreased mortality in patients with lung cancer [17]. Environmental and geographic factors were shown to play a role in development of dermatomyositis and polymyositis in different types of cancer. For example, nasopharyngeal cancer is common among Chinese and Korean patients with dermatomyositis and polymyositis while seldom in Jordan's population.

The incidence of SS is associated with a risk of malignancy, especially of the lymphatic system. Patients with that disease have a 10-fold to 44-fold greater risk of developing malignant lymphoma than the healthy population; among this group of malignancies the most common are mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma and marginal zone lymphoma, which account for 90% of the lymphomas developed in SS [18]. SS is also associated with an increased risk of multiple myeloma and lung cancer. The latter is 5 times more common in SS. A nationwide retrospective case-control study in Taiwan showed that patients with SLE and SS have a significantly increased risk of nonmelanoma skin cancer [19]. Decades of research on the association of SLE with cancer provide interesting data. While SLE is associated with a 4-fold increased risk of non-Hodgkin lymphoma, some studies report a decreased risk of female hormone-dependent cancers: breast, ovarian and endometrial [20–22]. Several studies also reported increased risk of cervical, vulva/vaginal, head and neck, thyroid, bladder and kidney, liver and non-melanoma skin cancer in patients with SLE [20, 21, 23–27]. The risk of malignancy in scleroderma has been described in three meta-analyses [28–31]. Onishi et al. examined 6641 people with scleroderma from Australia, northern Europe, Taiwan and the United States and showed an increased risk of lung, liver and hematologic cancers overall, as well as an increased risk of bladder cancer in women and nonmelanomatous skin cancer in men [29]. Similar results were observed in meta-analysis by Zhang et al. [30]. The authors observed increased cancer risk for lung cancer, hematopoietic cancer and non-Hodgkin lymphoma. The largest meta-analysis to date was conducted by Bonifazi et al. [31]. This meta-analysis was based on 16 observational studies and included publications presented by two earlier mentioned research groups. Investigators have demonstrated the risk of lung cancer and hematologic malignancies in patients diagnosed with scleroderma.

The idiopathic inflammatory myopathies (IIMs) are multisystemic diseases that include different systemic autoimmune rheumatic diseases such as: polymyositis (PM), adult dermatomyositis (DM), necrotizing myopathy (NM), myositis associated with another autoimmune diseases, cancer-associated myositis, juvenile myositis (JDM) and inclusion body myositis (IBM) [31]. The association between IIMs and cancer development is described in many large population studies [33–37] and is strong for patients with DM and less for PM, uncertain for NM or IBM, and not present with JDM. Clinical risk factors for cancer development include: age over 50 years, male gender, dysphagia, cutaneous necrosis, ulceration and vasculitis, sudden onset of myositis, refractory myositis, abnormalities in laboratory tests, especially concerning markers of inflammatory process [38–44].

Special attention is paid to targeted oncology therapies as they are associated with rheumatic immune-related adverse events (irAEs), estimated to be 5–10% in cancer patients tre-

ated with immune-checkpoint inhibitors (ICis) [45]. The most frequent rheumatic irAEs are: arthritis (1–7%), sicca (1.2–24.2%), myositis (0.4–6%) and polymyalgia rheumatica (0.2–2.1%). Less commonly observe syndromes are: de novo onset of sarcoidosis, vasculitis, lupus, antiphospholipid syndrome, scleroderma-like syndromes, bone abnormalities [45].

Screening for malignant diseases

Some authors point out that patients treated for rheumatic diseases should be monitored for the development of possible malignancies. The issue of screening for malignant diseases in patients with diagnosed rheumatic disease is at least debatable. In general, the number of cancer types for which screening is justified is small. In addition, the highest incidence of cancer and rheumatic diseases is observed in the elderly, but current recommendations and guidelines do not provide screening tests for people over 65 years of age. Nevertheless, there are reports in the literature recommending certain examinations to be performed in patients after antirheumatic treatment in search of possible neoplastic disease. This is difficult because it is unclear what such monitoring should look like, especially since most of the described cancers do not involve screening for these diseases in potentially healthy, non-cancerous individuals. Moreover, the most frequently diagnosed neoplastic diseases arising in the course of antirheumatic therapy (for example lymphoid malignancies, bladder cancer) are not screened in the healthy population. Also, it is not known which examinations at what time after the completion or duration of antirheumatic therapy should be done and whether all or only a selected group of patients should be screened for the presence of neoplastic diseases. What is more, screening procedures may vary in different countries. Therefore, instead of carrying out screening tests, which do not exist for certain diseases, one should pay attention to such symptoms as, for example: weight loss, sub-febrile states, enlarged lymph nodes (lymphoid tumors), hematuria (bladder cancer). It seems that in the absence of standards for treatment, guidelines and recommendations for screening patients with rheumatic diseases for neoplastic diseases should be developed. Such standards arguably should look similar to, for example, genetic syndromes leading to colorectal cancer, where specific screening tests are performed in the appropriate time sequence. A proposal for such an algorithm procedure was presented by Moghadam-Kia and coauthors for IIMs. This scheme recommends three types of patient screening for cancer depending on the degree of risk. For patients at high risk, intermediate risk, and low risk, comprehensive screening, enhanced screening, and basic screening are recommended, respectively [32]. For high risk patients, screening should be performed annually for three consecutive years after IIMs diagnosis and for enhanced and basic screening, testing should be performed only once at baseline. The basic screening includes routine blood tests,

chest radiograph, age-appropriate screening (colonoscopy, mammography, cervical cytology, PSA). The enhanced screening includes basic screening and consideration of one or more of the following evaluations: computed CT scanning of the chest, abdomen and pelvis, gynecologic/pelvic ultrasound examination in women and testicular ultrasound examination and tumor markers in men. The comprehensive screening includes basic or enhanced screening with consideration of PET-CT scanning of the chest, abdomen, and pelvis [32].

It is generally believed that an intensive diagnostic work-up for neoplastic diseases in rheumatic patients should not be performed unless symptoms clearly indicate the development of neoplastic disease. Markers – especially AFP, PSA, CA-125, CA-19-9 and CA-3 – have low sensitivity and specificity for cancer screening in patients with rheumatic diseases. Moreover, the recommended determination of tumor markers is not justified as they serve to monitor the treatment of cancer and not its diagnosis. It is not uncommon to find elevated tumor markers in patients treated for rheumatic diseases without coexisting neoplastic diseases [46]. Tumor-associated antigens (TAA) may be elevated in rheumatoid arthritis (RA), rheumatic musculoskeletal diseases (RMDs), systemic sclerosis (Ssc), and systemic lupus erythematosus (SLE) [44, 46–52]. The misleading concept of using markers in cancer screening is particularly evident in IIMs, where despite initial reports of the role of markers, current studies do not support their role in cancer detection [39, 52].

Conclusions

In the search for associations between cancers and rheumatic diseases, there is a need to construct methodologically valid studies based on a large patient populations. In the absence of clear recommendations for cancer screening of patients with rheumatic diseases, there is a need to develop guidelines for screening.

Conflict of interest: none declared

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