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Review

Cancer and autoimmune diseases

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ABSTRACT

Purpose of review: The association between autoimmunity and cancer is well established. Cancer has been implicated in some autoimmune disorders (AID), such as scleroderma and myositis. On the other hand, many autoimmune disorders and immunosuppressive therapy, have been linked to an increased risk for cancer. We reviewed the accumulating data on the association between autoimmunity and cancer during the past three years, with an emphasis on large cohorts, as well as concept changing discoveries in the association of cancer and auto-immunity.

Recent findings: Recent published data from large registries and databases have changed our perspective on the association of AID and cancer, as well as the presumed association between anti-tumor necrosis factor (anti – TNF) therapy and certain malignancies, suggesting a small to no increase in almost all types of cancers. Similarly, the increased risk of malignancies in some AID, such as Sjogren's syndrome (SS) and lupus, may be different from previous estimations. New associations with malignancies were discovered, such as IgG4 related disease, Behcet's and sarcoidosis, which were not clearly associated with cancer in the past.

These newly described associations may have clinical implications and contribute to our understanding of both autoimmunity and cancer.

Similarly, we reviewed studies of autoimmunity secondary to malignancy, and the concomitant appearance of cancer with autoimmune disease, such as the discovery of a specific mutation in scleroderma (SS) patients that developed cancer, which establishes the association between these disorders and sheds light on the pathology behind this association.

Contents

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1. Introduction

The association between cancer and autoimmune disorders (AID) is bidirectional. On one hand, an increased risk of malignancies, both hematological and non-hematological, has been observed in different autoimmune disorders. On the other hand, some malignancies may increase the risk of developing an autoimmune disorder. Furthermore, some cancers may present with clinical features resembling an autoimmune disorder. This review discusses the association of malignancies with common autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), inflammatory myopathies (IM), scleroderma (Sc), vasculitis (Vs) and other AID. This topic has been reviewed previously [1], and this article is an update of this topic reviewing literature published in the past two years.

2. Rheumatoid arthritis

Early studies have suggested an increased prevalence of malignancies among RA patients. The pathogenesis of RA involves a dysregulation of different aspects of the innate immune system including cytokines and cells that have been implicated in tumor formation [2], suggesting that the dysregulated immune system may be pro-oncogenic. Over the years, RA was associated with an increased risk of both hematological and solid malignancies [1]. An increased risk of cancer was also implicated in the treatment of DMARDs and biologic therapy.

Large trials assessing the association of RA and its treatment with cancer among different populations have been published in the past years (Table 1). Recently, a retrospective Korean cohort study [3], following 2104 RA patients over a mean follow-up duration of 7.4 years and 17,436 person years, showed that RA patients have an increased risk of non-Hodgkin's lymphoma (standardized incidence ratio (SIR) = 3.387, 95% CI = 1.462–6.673), but a lower risk for gastric cancer (SIR = 0.663, 95% CI = 0.327 to 0.998). Similarly, a larger nationwide Japanese cohort database [4], between 2003 and 2012, composed of 66,953 patient-years yielded an overall incidence of malignancies in patients with RA which was slightly lower than in the general population (SIR 0.89, 95% CI 0.82–0.97). A reduced risk was noted in malignancies of the rectum and the kidney in males, in stomach and rectal cancer in females, and in liver malignancies among both males and females. Nevertheless, the risk of lymphoma was significantly higher (SIR 3.43, 95% CI 2.59–4.28) among RA patients of both sexes, but the incidence of leukemia was markedly reduced in RA females [5].

Similar results were observed in a nationwide dynamic cohort study in Taiwan [6] following 30,504 patients with no history of cancer who were newly diagnosed with RA between 1996 and 2008 and followed up to 2010 (225,432 person-years of follow-up). The overall risk for malignancy was reduced (SIR = 0.93, 95% CI 0.88–0.97); among site-specific solid cancers, only colorectal cancer was significantly reduced (SIR = 0.71, 95% CI 0.61–0.82), while an increased risk was shown for Hodgkin's lymphoma (SIR 3.31, 95% CI 1.24–8.81) and NHL (SIR 3.18, 95% CI 2.64–3.83). Further analysis of this cohort revealed increased risk for both lymphoid and myeloid malignancies in male and for lymphoid malignancies female RA patients.

Surprisingly, another recently published study from a cohort of 3499 Danish RA patients [7] found that neither recent onset nor long-standing RA was associated with the incidence of solid tumors or lymphoproliferative malignancies after adjusting for confounders, but the follow-up period in this cohort was only 4 years.

In a similar accord, a nationwide population based prospective cohort study from Sweden found that RA patients who have not been treated with biological drugs do not exhibit an increased risk of melanoma compared with the general population. Yet another study from Sweden [8], following 125,117 RA patients from 1964 to 2010 (1,212,967 person years, mean follow-up 9.7 years) found a 2-fold increase in NHL. Analysis from the Swedish register also found [9] higher rates of cytology screening, CIN I-II, and CIN III among biologic naive RA patients compared to the general population cohort, albeit no difference in invasive cervical cancer rates. Similar results were found in a smaller Canadian prospective study [10] Conversely, an increased risk of cancer was observed among biologic-naïve RA subjects receiving non-biologic DMARD therapy recruited to the British register BSRBR from 2002 to 2009 [11]. This cohort comprised 3771 RA patients (13,315 person-years of follow-up) revealed an overall increased risk of cancer (SIR = 1.28, 95% CI 1.10–1.48). An increased risk was noted in lung cancer (SIR 2.39, 95% CI 1.75, 3.19), Hodgkin lymphoma (SIR 12.82, 95% CI 4.16, 29.92) and non-Hodgkin lymphoma (SIR 3.12, 95% CI 1.79, 5.07), while the risk of prostate cancer (SIR 0.35, 95% CI 0.11, 0.82) and gynecological cancers (SIR 0.35, 95% CI 0.10, 0.90) was reduced. Current or previous smoking increased the risk 2-fold.

The discrepancy between these results could be explained by an inter-country variance in environment, genetic risk factors, the prevalence of comorbidities, patient compliance and prevention [12]. For example, a meta-analysis performed by Tian et al. [13] found no increased breast cancer risk in RA patients However, the subgroup analysis showed that while the risk was reduced in Caucasians (SIR = 0.82, 95% CI = 0.73–0.93), non-Caucasians exhibited an increased risk (SIR = 1.21, 95% CI = 1.19–1.23). In the same meta-analysis, hospital-based case subjects also showed a reduced risk, suggesting that these subjects also showed a reduced risk severity of the disease and its course may modify the risk of cancer.

Smitten et al. [14]have conducted a meta-analysis in 2008 reviewing incidence of malignancies in RA patient. This was recently updated by Simon et al. [15], supporting their previous data showing increased risk for lymphomas, and to a lower degree, lung cancer, but not for other malignancies. This observational meta-analysis reviewed published studies between 1 January 2008 and 30 November 2014, found a modest increased risk in overall malignancy. An increased risk was found for lymphoma and lung cancer compared with the general population, while colorectal and breast cancers showed a decrease in risk. Cervical cancer, prostate cancer and melanoma appeared to show no consistent trend in risk in this meta-analysis.

Similarly, Askling et al. compared different registries across the world, finding high consistency in overall cancer rates, excluding non-melanoma skin cancer, across 5 large registries from the US, UK, Japan Sweden and others, following age/sex standardisation. SIR of overall malignancy excluding NMSC varied from 0.56 to 0.87 per 100 person-years.

2.1. Cancer outcomes

Besides the risk for cancer, RA also has an impact on cancer survival in RA patients with cancer. Mortality was increased by 40% and 50% respectively in elderly patients with RA who developed breast or prostate