Rheumatic disease and malignancy

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Abstract

Background: A number of rheumatic disorders are associated with an increased risk for various malignancies. The reasons for this risk are not well defined. Furthermore, pharmacologic therapy of rheumatic diseases may increase the risk of malignant disease.
Objective: The aim of this literature review is to address the various rheumatic diseases and their pharmacologic therapy that are associated with an increased risk of malignancy.
Data source: The literature review uses medical science based literature published locally and internationally on the risk of malignancy in patients with rheumatological diseases and the use of antirheumatic medications.
Conclusion: Individual rheumatic diseases are associated with increased risk of particular malignancies. A number of the pharmacologic therapies used for the treatment of rheumatic diseases may increase the risk of malignancy. In these patients who are at risk for cancer related to their autoimmune disease, age- and sex-appropriate screening should be performed, and additional screening may be added based upon the risk factors of an individual patient.

Key words: Rheumatic diseases, Cancer, Antirheumatic medication, Malignancy, Screening

Introduction

There are complex bi-directional relationships between rheumatic diseases and cancer. Certain rheumatic diseases like inflammatory myositis, systemic lupus erythematosus and Sjogren's syndrome are associated with an increased risk of malignancy. In addition, treatments for rheumatic diseases may also increase malignancy risk[1]. Specific rheumatic diseases and risk of malignancies; and the contribution of antirheumatic drug therapies to such risk will be reviewed in this article.

Rheumatic diseases with associated malignant disorders

The rheumatic diseases associated with an increased risk for various malignancies include rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis (scleroderma), myositis (polymyositis, dermatomyositis), Sjögren's syndrome, and ANCA-associated vasculitis. The reasons for this increased risk is not well defined, but likely to involve chronic inflammation and autoimmunity[2].

Dermatomyositis and polymyositis

Dermatomyositis is associated with a 6-fold increased risk of malignancy while polymyositis is associated with a 2 fold increased risk of malignancy[3]. Patients with anti–TIF1-γ and anti–nuclear matrix protein–2 have the highest risk. The risk is highest in the first 2 years after diagnosis, gradually decreasing with time[4]. Numerous cancers have been associated with dermatomyositis, particularly breast, ovarian, lung, haematologic and nasopharyngeal cancers especially in Asian population[5]. Clinical features of dermatomyositis that increase the risk of malignancy include male sex, older age, severe skin manifestations, dysphagia, resistance to treatment, history of prior malignancy and absence of interstitial lung disease[6].

Rheumatoid arthritis

The initial link between RA and cancer was established by Isomaki *et al*[7]. He established that patients with RA had a higher incidence of lymphomas, leukemias and myeloma. Numerous other studies and meta-analyses have also shown an increased incidence in lung cancer but a reduced incidence of breast and colon cancer in patients with RA. The standardized incidence ratio of all malignancy risk, lymphoma, lung cancer, breast cancer and colon cancer was 1.09, 2.46, 1.64, 0.86 and 0.78 respectively[8].

The increase in risk for cancers can be attributed to shared risk factors between RA and cancer. For example smoking increases the risk of both RA and lung cancer[9]. RA, in itself can lead to increased risk of lymphoma because of increased chronic immune stimulation in lymphomagenesis[10]. The observation of a reduced risk of colon cancer may be due to the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in RA. It is known that NSAID use is associated with reduced risk of colon cancer[11].

Systemic Lupus Erythematosus (SLE)

There is increasing evidence to suggest that patients with SLE have a slightly higher overall risk of malignancy. A large multisite cohort study by Bernatsky *et al*[12] reported an SIR of 1.14. Patients with SLE are at a moderately increased risk of haematologic malignancies, particularly non-Hodgkin's lymphoma with an SIR of 3.02[12]. Furthermore, these patients presented with advanced stages and extra nodal disease and had poor outcomes despite aggressive treatment. Several individual cohort studies that were reviewed by Choi *et al*[13] have reported increased risk of lung, liver, head and neck, thyroid, vaginal/vulvar, cervical (cancerous and pre-cancerous), dermatologic, bladder or renal, anal, and pancreatic malignancies in patients with SLE.

The factors that potentially mediate or are thought to increase the risk of malignancy in SLE include use of cyclophosphamide[14], autoantibodies such as antiphospholipid antibodies[15] and chronic immune dysregulation[16]. There is a possibility that the increased prevalence of certain cancers in patients with SLE may be due to increased exposure to known environmental risk factors such as smoking and oncogenic viruses[13].

Sjogren's Syndrome (SS)

Monoclonal gammopathies occur in at least 20% of patients with Sjogren's syndrome[17]. It is usually associated with hypergammaglobulinemia, cryoglobulinemia, or haematologic neoplasia. SS patients with monoclonal gammopathies have an increased incidence of lymphoma[18]. In addition, the risk of multiple myeloma and Waldenstrom macroglobulinemia is also increased[19].

Patients with SS have the highest risk of non-Hodgkin's lymphoma amongst all other rheumatologic diseases. In a pooled analysis, the relative overall risk of NHL was 6.6[20], with a life time risk that is 44 times higher than that of the normal population[21]. Persistent salivary gland enlargement is the most important clinical risk factor, while other risk factors includes cutaneous vasculitis, lymphadenopathy, splenomegaly, cryoglobulinemia, and glomerulonephritis. The transition from SS to lymphoma is a process that requires many years[22].

Extra nodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) involving the parotid gland is the most common histologic subtype in SS[20]. Other types of NHL that are common in SS include diffuse large B cell lymphoma and nodal marginal zone lymphoma[23]. The MALT lymphoma is of low grade and indolent with a 15 year survival to 80%[24]. SS patients with persistent salivary gland enlargement should be investigated for lymphoma.

Systemic sclerosis (scleroderma)

Several reports have shown an increased risk of cancer in patients with scleroderma[25,26]. In a nationwide population-based cohort analysis from Denmark, the most frequent cancers were lung, haematologic, esophageal and oropharyngeal carcinoma[27]. The cause of cancer in SSc is not well understood, however it has been observed that patients with autoantibodies to RNA polymerase I/III are at a higher risk of developing cancer[28].

Systemic vasculitis

The malignancies associated with systemic vasculitis include hairy cell leukemia and myelodysplastic syndrome. About 40% of the patients with systemic vasculitis have concurrent malignancy. Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis carries a 1.6 to 2.0 higher risk for developing malignancy[29].

Polymyalgia rheumatica / giant cell arteritis

There is an increased risk of malignancy particularly in the first 6 – 12 months after diagnosis[30]. In some cases, polymyalgia rheumatica may be the initial manifestation of malignancy[31].

Remitting seronegative symmetrical synovitis with pitting edema (RS3PE)

RS3PE usually occurs in adults and presents with edema of the hand and feet along with synovitis. About 15% – 30% of patients with RS3PE have concurrent malignancy ranging from haematologic to solid malignancies[32].

Paraneoplastic polyarthritis

Symmetric polyarthritis mimicking rheumatoid arthritis can occur as a paraneoplastic phenomenon. Paraneoplastic polyarthritis is more common in male, has an asymmetric onset and associated with high markers of inflammation distinguishing it from RA. It is mostly seen in patients with myelodysplastic syndrome[33].

Palmar fasciitis

This is a rare disorder that is associated with numerous malignancies. The most frequently reported is ovarian cancer but other sites have also been reported. Treatment of the associated malignancy has led to improvement of some cases[34].

Eosinophilic fasciitis

This is an uncommon condition characterized by woody induration of the limbs with peripheral eosinophilia. In 10% of the patient there is usually an underlying haematologic disorders like lymphoma and leukemias[35].

Erythromelalgia

This is a rare syndrome that is associated with myeloproliferative disorders like polycythemia rubra vera in 10% of the patients[36].

Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy is usually associated with lung cancer[37]. About a third of the patients with lung neoplasm have digital clubbing. It is most frequently associated with peripherally located adenocarcinoma of the lung and more common among men[38]. Treatment of the lung cancer may lead to regression. Bone scintigraphy is a sensitive way to detect skeletal involvement with the disorder. Particular attention to the chest should be paid to a patient presenting with hypertrophic osteoarthropathy as the most common cause of acute hypertrophic osteoarthropathy is a lung neoplasm.

Antirheumatic medication and risk of malignancy

Cyclophosphamide

Cyclophosphamide increases the risk of leukemia, skin cancer and urinary bladder cancer. This is due to direct chromosomal damage and decreased immune surveillance. The most important risk factor is the duration of the treatment, with most cancers occurring in patients treated for more than two years[39]. A long term follow up population-based cohort study found that patients treated with cyclophosphamide had a higher rate of malignancy. The risk was highest for patients who had a cumulative dose of over 36 grams except for squamous cell carcinoma, where the risk increased even at cumulative dose of 10 grams[40]. In patients with Granulomatosis with Polyangiitis (GPA), myelodysplastic syndrome occurred in 8% of patients who had prior exposure to cyclophosphamide and this increased to 13% who had a cumulative dose of more than 100 grams[41].

The risk of bladder cancer is increased with oral cyclophosphamide and likely dose dependent with a standardized incidence ratio of 4.30[40]. The increased risk may be sustained for years even after discontinuation of cyclophosphamide. In a retrospective study of 145 patients with GPA who had been treated with oral cyclophosphamide for at least one year, there was a 5% incidence of bladder cancer at eight years of follow up. This incidence increased to 16% at 15 years of follow up. Two thirds of the patients who developed bladder cancer had had a cumulative dose of more than 50g and had at least one episode of either microscopic or macroscopic haematuria[42]. The tumours tend to be biologically aggressive, mostly grade 3 or 4 transitional cell carcinoma[43].

Azathioprine

There is a possible but small increased risk of malignancy in rheumatoid arthritis patients treated with azathioprine. However, this risk was not significant when adjusted for confounding variables. There is an absolute increase of 1 case per 1000 patients years of exposure for lymphoproliferative malignancy after a 20 year follow up[44].

Methotrexate

A large observational cohort found a non-significant small increase of lymphoproliferative malignancy in patients taking low dose methotrexate. The lymphoproliferative malignancy are usually of B cell origin and are associated with latent Epstein Barr virus infection[45]. Another prospective study from France, described 25 cases of lymphoma in patients with RA who had been treated with methotrexate for three years. Among them, were seven cases of Hodgkin's disease with an SIR of 7.4[46]. Some of these tumours may regress on discontinuation of methotrexate and may not require further chemotherapy. However continued vigilance is necessary as relapse can occur[47].

Mycophenolate

There has been one reported case of CNS lymphoma that occurred in a patient taking mycophenolate monotherapy for myasthenia gravis[48]. In addition, MMF prescribing information has a specific warning label about increased risk of lymphoma as a result of immunosuppression and avoiding MMF in patients with prior history of lymphoma.

Tumour necrosis factor alpha inhibitors

In general, there is a preponderance of evidence that TNF inhibitors do not increase the risk of most solid tumours except skin cancers. However, uncertainty remains. Some meta-analysis of clinical data have found an increased risk but observational data, particularly from registries, have not been able to confirm these findings[49,50]. This discrepancy may be due to more complete recording of malignancies in clinical trials than in routine practice.

The overall risk of lymphoma is not increased. However, a small number of hepatosplenic T cell lymphoma cases, a very rare form of non-Hodgkin's lymphoma, has been associated with use of TNF inhibitors. Most of these cases have occurred in young male with inflammatory bowel disease who had also received concurrent thiopurines[51]. However, there is a slightly increased risk of cervical cancer and non-melanoma cancer in patients using TNF inhibitor[52,53]. The combination of cyclophosphamide and TNF inhibitor heightens the risk of cancer, hence combination of these two drugs is not encouraged[54].

Other biologic DMARDS

The other biologic DMARDS have not been studied. Furthermore, these drugs have been marketed recently and registry data are still immature to allow any firm conclusion. In a meta-analysis involving all biologics, there was no overall increase risk of malignancy with any of the biologic DMARD. However, only four studies were included in the meta-analysis[55].

In a long-term safety report of rituximab, which included 3500 patients with RA who had been followed up for 11 years, did not indicate an increased risk of malignancy when compared with the general US population[56]. Similarly, analysis of eight clinical trials revealed no increased risk of malignancy in patients who were given abatacept[57]. However, long term extension trials and combined analysis of tocilizumab suggest that tocilizumab use may be associated with an increased risk of malignancy. Updated data showed an SIR of 1.36 and 1.81 in comparison with SEER database and GLOBOCAN data respectively[58]. On the contrary, a Japanese study reported an SIR of 0.79. This study also reported an SIR of 3.13 for lymphoma with reference to Japanese population[59].

Screening for malignancy in rheumatic disease

There are controversies on how to appropriately screen patients with rheumatological diseases for an underlying cancer. The most important step is ensuring that age- and sex- appropriate cancer screening has been done regardless of the rheumatological disease the patient is suffering from. For certain patients with rheumatological diseases known to be associated with increased risk of cancer like systemic sclerosis or myositis, their cancer screening should be based according to their risk of developing cancer. For example, in myositis, patients with antibodies to nuclear matrix protein 2 and Transcriptional Intermediary Factor 1 (TIF1) gamma are more likely to have cancer within three years of disease onset (60) accurate identification of patients likely to harbor cancers is important. Using immunoprecipitations from radiolabeled cell lysates, several groups recently showed that anti-transcription intermediary factor 1γ (anti-TIF-1γ. Similarly, in SSc, patients with anti-RNA polymerase III or anti-RNPC3 antibodies and diffuse SSc are more likely to have cancer-associated SSc[61].

Conclusion

Individual rheumatic diseases are associated with increased risk of particular malignancies. A number of the pharmacologic therapies used for the treatment of rheumatic diseases may increase the risk of malignancy. In these patients who are at risk for cancer related to their autoimmune disease, age- and sex-appropriate screening should be performed, and additional screening may be added based upon the risk factors of an individual patient.

Conflict of interest

The authors declare that there is no conflict of interest.

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