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Malignancy in Systemic Lupus Erythematosus: What have we learned?

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Abstract

What have we learnt about cancer risk in systemic lupus erythematosus (SLE) over the past decade? One important lesson is that data do confirm a slight increased risk in SLE for all cancers combined, compared to the general population. However, it is clear that this is largely driven by an increased risk for hematological malignancies, particularly non-Hodgkin's lymphoma (NHL), although Hodgkin's lymphoma may be increased as well. In addition, there is evidence for a moderately increased risk of lung cancer, and possibly for rarer cancer types, such as hepatobiliary and vulvar/vaginal malignancies.

Unfortunately, the most clinically relevant question, the mechanism underlying the association between cancer and SLE, remains largely unanswered. Key issues remaining under study relate to the links between cancer risk, SLE disease activity, and medication exposures. Much of the recent data suggest that disease-related factors may be at least as important as medication exposures for certain cancers, such as NHL. The independent effects of drug exposures versus disease activity in mediating cancer risk in SLE remain unknown. Work is in progress to further elucidate these important issues.

Meanwhile, there is good evidence that cervical dysplasia is increased in women with SLE. This may be mediated by decreased clearance of the human papilloma virus, which some suggest is an innate characteristic of SLE patients. However, an increased risk of cervical dysplasia is also associated with immunosuppressive medication exposures, particularly cyclophosphamide. For these reasons, it is important that women with SLE follow established guidelines for cervical cancer screening.

Keywords

Malignancy; cancer; systemic lupus erythematosus; SLE; lymphoma; NHL

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The association between cancer risk and autoimmune disease has been under scrutiny for decades(1). This review article summarizes what we have learnt to date, regarding the links between systemic lupus erythematosus (SLE) and malignancy.

Cancer Risk in SLE Relative to the General Population

For some time, there was significant debate as to whether persons with SLE did in fact have an increased risk of cancer compared to the general population. Of particular concern were haematological malignancies (particularly lymphoma) as well as lung cancer, two types of cancer that have been demonstrated to be elevated in other autoimmune rheumatic diseases, such as rheumatoid arthritis (RA)(2).

In the past decade, several large studies have defined the magnitude of cancer risk in SLE. A Swedish study, using a lupus cohort (N=5,175) assembled from hospital discharge data, established a relative risk of cancer in SLE, compared to the general population, of 1.25 (95% confidence interval [CI] 1.14, 1.37)(3). This was primarily driven by a higher incidence of non-Hodgkin's lymphoma (NHL) in SLE, which was increased almost 3-fold compared to the general population (relative risk of 2.86, CI 95% 1.96, 4.04). This study also demonstrated an increased risk of lung cancer (relative risk of 1.73, CI 95% 1.25, 2.32) and a trend towards an increased risk of squamous cell skin cancer (relative risk 1.53, CI 95% 0.98, 2.2).

Given some lack of confidence in the work conducted on a hospital-based lupus cohort, there has been great interest in the recent results of a larger (N=9,547) multi-centre international cohort study(4). This was completed under the umbrella of the Systemic Lupus International Collaborating Clinics (SLICC) research group, with the collaboration of the Canadian Network for Improved Outcomes in Systemic Lupus. The patients in this multi-centre all had a clinically confirmed diagnosis of SLE, and were ethnically diverse. Standard incidence ratio (SIR) estimates were calculated, as the ratio of observed to expected cancers, based on data from regional cancer registry linkages.

The multi-centre cohort data confirmed a small increase in all cancers combined, with an SIR estimate of 1.15 (95% CI 1.05, 1.27). A dramatic increased risk for hematological malignancies was also confirmed, particularly for NHL, where the SIR was 3.64 (95% CI 2.63, 4.93). The data similarly demonstrated an increased risk of lung cancer (SIR 1.37, 95% CI 1.05, 1.76) and hepatobiliary (SIR 2.60, 95% CI 1.25, 4.78) malignancies. Non-melanoma skin cancer was not assessed in this study, since this type of malignancy is not predictably captured by cancer registries.

Interestingly, in the multi-centre cohort study, there was suggestion of a decreased risk in SLE (compared to the general population) of some hormone-sensitive malignancies such as breast cancer (SIR 0.76, 95% CI 0.60, 0.95) and endometrial cancer (SIR 0.36, 95% CI 0.13, 0.78). Whether there was some systematic bias in case ascertainment for these cancers, or whether some unknown factors were at play (perhaps lower endogenous estrogen exposure in some populations of women with SLE(5)), is unknown. In contrast, there was a trend towards more vulvar and vaginal malignancies than expected (4 observed versus 1.7 expected, for an SIR of 2.35 (0.39, 3.10). The recent report of Patel et al emphasized an increased risk in SLE not only for hematological and lung cancers, but for hepatobiliary and vulvar/vaginal cancers(6). Unfortunately, the sample of Patel et al was assembled from administrative hospitalization data; such methodology is likely to introduce bias(7), so the usefulness of that data is limited.

Data from the multi-centre cohort also suggested an association of white race with total cancer risk in SLE, although the specific risk for lymphoma appeared to be fairly uniformly increased across racial and ethnic groups(8). One interpretation is that race-related effects in SLE may be more important for non-hematological cancers, such as breast cancer(9). The mortality risk

due to cancer in SLE has also been evaluated in the multi-centre SLE cohort(10), demonstrating an increased risk for NHL (standardized mortality ratio [SMR] 2.8, 95% CI 1.2, 5.6) and lung cancer (SMR 2.3, 95% CI 1.6, 3.0).

More on Lupus and Hematological Cancer Risk

Evidence for an association between SLE and NHL was also suggested by Smedby et al, in a population-based case-control study. Here, the frequency of autoimmune diseases among NHL patients from the general population was assessed and compared with matched population-based cancer-free controls(11). Over 3,000 NHL cases were studied, and of these, eight had a prior history of SLE, whereas only two of the matched cancer-free controls reported a history of SLE. The adjusted odds ratio (OR) for SLE and NHL was 4.6 (95% CI 1.0, 22).

Given the growing evidence linking lymphoma and SLE, there have been several studies of lymphoma histology and presentation in SLE, in an effort to better define the pathophysiology of the association. In the above-mentioned study of Smedby et al, the association of SLE and NHL seemed greatest for the diffuse large B-cell lymphoma subtype(11). Moreover, two other studies confirm these findings(12–14). The diffuse large B cell subtype makes up about 30% of all NHL lymphomas in the general population, but represented more than half of the NHL lymphomas of known cell type in the multi-centre cohort SLE sample (a difference of 22.4%, 95% CI 2.2 to 41.8%)(13).

Smedby et al suggested that there was a tendency for persons with SLE to present with lymphoma in extra-nodal sites, which is a marker of poor lymphoma prognosis in general. Two other recent analyses of lymphoma in autoimmune rheumatic diseases, including SLE, also suggested that in these cases, the patient often presents with extra-nodal disease and/or in advanced stages(14;15). One study demonstrated a bimodal pattern for mortality risk in SLE patients with NHL, with a number of patients succumbing early after lymphoma diagnosis, and the remainder experiencing quite reasonable survival rates(14). In general, these data also confirm that Epstein-Barr virus (EBV)-associated lesions make up only a small fraction of lymphomas in autoimmune rheumatic disease like SLE.

Regarding other hematological cancers besides NHL, a study using administrative data from the general population of Denmark and Sweden(16;17) reported that the incidence of HL was associated with a past history of SLE (OR 5.8, 95% CI 2.2 .15.1). This concurs with a recent meta-analysis which calculated a pooled SIR of 3.16 (95% CI, 1.63, 5.51) for HL risk in SLE versus the general population(18). Analyses of Swedish administrative data suggested that a family history of SLE was a risk factor for multiple myeloma (OR = 2.66; 95% CI 1.12, 6.32) (19). However, a recent case-control study from the United States did not identify a past history of SLE as one of the risk factor for the development of multiple myeloma(20). A study of SLE patients with and without monoclonal gammopathy, based in a very large North American lupus cohort, demonstrated no differences in clinical features or medication exposure, and none of the SLE patients with monoclonal gammopathy had multiple myeloma(21).

Regarding clinical correlates of lymphoma risk in SLE, a recent Swedish case-control study in SLE provided interesting evidence that specific clinical characteristics are associated with NHL development(14). Of significance was a history of hemolytic anemia, which was associated with a crude relative risk (RR) of 3.2 (95% CI 2.0, 5.0). (Interestingly, autoimmune hemolytic anemia has also been associated with diffuse B-cell NHL in the general population (22).) In the Swedish case-control study, lupus anti-coagulant or anti-phospholipid antibodies conferred a crude RR of 2.0 (95% CI 1.0, 4.2) for NHL in SLE. The authors considered that in some cases, these clinical features (hemolytic anemia, anti-phospholipid antibodies, etc.) may have themselves been a paraneoplastic manifestation of a B-cell malignancy. Thus, the extent to which these characteristics help predict lymphoma risk in SLE is unclear.

In the Swedish SLE study subjects, additional clinical features that were seen more often in the NHL cases compared to the controls were anti-Ro/anti-La positivity (crude RR 2.0, 95% CI 1.0, 4.1) and clinical characteristics suggestive of secondary Sjogren's syndrome (sicca symptoms and/or salivary gland swelling, crude RR 2.7, 95% CI 1.5, 5.0). To date, this is the strongest suggestion that secondary Sjogren's syndrome may drive some of the lymphoma risk in SLE. Of course the histology traditionally associated with primary Sjogren's syndrome is marginal zone-lymphoma of mucosa-associated lymphatic tissue (MALT), whereas diffuse large B-cell lymphoma is the predominant histological type in SLE. However, recent work suggested that both marginal zone lymphoma and diffuse large B-cell lymphomas may be increased in primary Sjogren's(22).

Characteristics of Lung Cancer Risk in SLE

The multi-centre international lupus cohort study demonstrated that SLE patients are at higher risk than the general population for lung cancer (SIR 1.37; 95% CI 1.05, 1.76). A review of the reported histology of the lung cancers from this study showed that the majority were adenocarcinoma, as is seen in the general population(23).

One study of lung cancers arising in various autoimmune rheumatic diseases (primarily systemic sclerosis, RA, and SLE) suggested that on average, such malignancies tend to arise late in the disease course (an average of 13.9, range 0–30, years after disease diagnosis). The majority of lung cancers in their sample were diagnosed at advanced stages (85% in stages III–IV) and had poor survival (median survival was 5 months, range 1–96)(24). This suggests a tendency towards delayed diagnosis of cancers occurring in autoimmune diseases, a phenomenon previously suggested in breast cancers in women with SLE(25), which is possibly due to neglect of cancer screening in the SLE population(26).

Smoking has been confirmed as an important etiologic agent for lung cancers in SLE (as in the general population). A recent case-cohort study in SLE found the lung cancer risk of lupus patients who smoked (compared to those who did not) to be increased almost four-fold (adjusted HR 3.6, 95% confidence interval, CI 1.32, 9.83). This underlines once again the universal importance of smoking cessation, particularly in chronic autoimmune disorders like SLE. Still, it is possible that shared genetic susceptibility may predispose an individual to both autoimmune disease and lung cancer. In fact, it is believed that smoking might mediate the risk of RA conferred by certain susceptibility genes(27;28).

Another theory is that lung cancer might be linked to autoimmune diseases like SLE, RA, and scleroderma through fibrotic lung disease, given the high lung cancer risk seen in idiopathic pulmonary fibrosis(29;30). Here, the proposed mechanism is that chronic inflammation due to chronic fibrotic lupus pneumonitis leads to extensive DNA damage and potentially, cancer (30). Lung cancer data from the multi-centre SLE case-cohort study did not strongly support this theory, as pre-existing lung damage (based on the Systemic Lupus International Collaborating Clinics [SLICC]/American College of Rheumatology [ACR] damage index scores) was only seen in one lung cancer case.

Is Cancer Risk in SLE Driven by Medication Exposures?

Unfortunately, the most clinically relevant question, the ***mechanism*** underlying the association between cancer and SLE, remains largely unanswered. A potential link between cancer risk and drug exposures in SLE remains difficult to establish definitively because of the close association between lupus disease activity and immunosuppressive use. Of note, it has been shown by several authors that the increased risk of lymphoma in SLE seems to be highest (relative to general population cancer rates) early in the disease(3;4). This may indicate that not all of the malignancy risk in SLE is driven by cumulative drug exposures. It is noteworthy

that in one study, the relative risk (in SLE compared to the general population) of some non-hematological malignancies (such as lung cancer and non-melanoma skin cancers) appeared to be most pronounced later (>15 years) in follow-up(3). This suggests the hypothesis that in SLE, lymphoma risk may be driven in large part by abnormal immune system activity early in the disease course, while other cancers (such as lung cancer and skin cancer) may be driven by other factors over the disease course.

In recent reviews of NHL arising in SLE and other autoimmune rheumatic diseases, a relatively low prevalence of immunosuppressive drug use has been noted(15;31). In the study by Smedby et al, five of the eight SLE cases with NHL were defined as having severe lupus (on the basis of at least one hospitalization for the disease, by self-report), but only one of these eight had a history of immunosuppressant medication exposures prior to the NHL development(11). This appears to suggest that NHL risk may be associated with lupus activity more than with drug exposures.

Some authors, studying general population samples, have suggested links between NHL and non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. However, these associations do not appear to be borne out, based on recent meta-analyses(32). Thus, the earlier suggested association may only reflect an underlying increased risk of lymphoma in patient populations that chronically use corticosteroids or NSAIDs, including those with autoimmune diseases such as RA or SLE. This may again point to theimportance of disease activity in driving NHL risk in persons with an underlying autoimmune disease.

A potential protective effect of anti-malarial agents against malignancy risk has been suggested by one group (33). Here, in a cohort of 235 SLE patients, Cox proportional hazards models, with cancer as the dependent variable, were developed. Covariates included demographics (age, year of lupus diagnosis, sex), initial SLICC/ACR Damage Index score, some drug exposures (anti-malarial drugs, azathioprine, cyclophosphamide, methotrexate) and smoking. The adjusted HR for cancer among users compared with non-users, suggested a marked protective effect of anti-malarial agents, although the confidence interval was very wide (HR 0.15, 95% CI 0.02 to 0.99). Unfortunately, in this study, anti-malarial exposure was classified as any use during the cohort follow-up (ever-never), which did not account for *when* the agent was initiated. This would result in significant misclassification of person-time in terms of exposure(34). In fact, in large studies in SLE(35) and RA(36) populations, with risk-set analyses to avoid misclassification of exposure, there was no demonstrated protective effect of anti-malarial agents.

To date, there are two large scale studies that have shed some light on these issues. In a recent case-control study from Sweden, the clinical features and drug exposures of 16 SLE patients who developed NHL were compared to 26 cancer-free control patients with SLE (matched on observation time and sex)(14). Regarding medication exposures, 44% of patients with lymphoma (N=7) had been treated with azathioprine or cyclophosphamide prior to their cancer, compared to 38% (N=10) patients without lymphoma. The crude RR for cyclophosphamide was 1.1 (95% CI 0.3–3.3) and for azathioprine it was 0.9 (95% CI 0.5–2.5). Unfortunately, the authors did not provide estimates adjusted for concomitant therapy or other covariates, and no correction was made for multiple testing. As this study was unable to control concomitantly for disease activity and drug exposures, two variables that are very tightly linked, conclusions derived from the study are limited.

To date, the most thorough assessment of cancer risk factors in SLE was based on further analyses of a sample from the previous multi-centre lupus cohort study(35). Here, the HR for cancer after exposure to an immunosuppressive drug was calculated, controlling for other medications (anti-malarial drugs, systemic glucocorticoids, NSAIDs, aspirin), smoking, age,

sex, race/ethnicity, geographic location, calendar year, SLE duration, and SLICC/ACR Damage Index scores. The adjusted HR for overall cancer risk after any immunosuppressive drug was 0.82 (95% CI 0.50–1.36). However, considering haematological cancers specifically, there was a suggestion of an increased risk after immunosuppressive drug exposures, particularly when these medication exposures were lagged by a period of 5 years (adjusted HR 2.29, 95% CI 1.02–5.15). It may be that cyclophosphamide is the driving force behind this risk; the adjusted drug-specific HR estimate for cyclophosphamide exposure was 3.55 (95% CI 0.94–13.37); for azathioprine, 1.02 (95% CI 0.34–3.03); and for methotrexate, 2.57(95% CI 0.80–8.27).

An important difference between the case-control study from Sweden and the multi-centre case-cohort study is that the Swedish studied focused on NHL, while the multi-centre study combined both leukemia and lymphoma in the analyses of hematological cancers. In studies of populations other than SLE, immunosuppressants have been linked with both lymphoma and leukemia, although alkylating agents (e.g. cyclophosphamide) may be more associated with leukemia, than lymphoma. Thus, a hypothesis could be that some hematological malignancies in autoimmune diseases may be caused by drugs like cyclophosphamide, but that for NHL risk, disease activity may be equally (or potentially, even more) important. Though EBV-driven lymphomas do not constitute the majority of hematological malignancies in autoimmune diseases like SLE, a reversible Hodgkin's lymphoma associated with EBV occurring during azathioprine therapy for SLE has been reported(37).

With the increased interest in immunosuppressive drug use and cancer risk, there is a chance of unwarranted hesitancy by both patients and physicians to use these agents. However, immunosuppressants can be life-saving in SLE, and have demonstrated benefits in terms of control of severe manifestations, and the prevention of important long-term sequelae, such as renal dysfunction in patients affected by lupus nephritis. Also, it should be recalled that the highest relative risk (RR) estimates (for patients with SLE compared to the general population) relate to relatively rare cancers, such as lymphoma. In contrast, almost all patients with severe SLE will suffer some damage either directly or indirectly related to lupus, if their disease is not well controlled. Thus, immunosuppressive drug use in SLE should be evaluated on a case-by-case basis, weighing the benefits incurred by controlling disease manifestations and preventing organ damage, against what is, practically speaking, a relatively small absolute risk of developing a malignancy. For example, when immunosuppressive agents are clearly indicated (such as for severe renal involvement), immunosuppressants should not be avoided for fear of malignancies. Since cyclophosphamide appears to be one of the greatest culprits in terms of drug exposures and cancer risk, we strongly endorse further efforts to find alternatives to this toxic but still useful (in the setting of severe disease) agent.

Hematological Malignancies and Inflammation

General support for the role of chronic autoimmunity and immune stimulation in haematological malignancy risk was suggested by several administrative database studies, which found increased risks (compared to the general population) for patients with a diverse group of autoimmune conditions(38;39). One caveat of their methodology was the construction of study samples using hospitalization data, as it is well known that hospitalized persons are more likely to be diagnosed with co-morbidity (including cancer) than the general population (40). One study found a higher risk of certain hematological malignancies and autoimmune disease, such as NHL with Sjögren's syndrome and SLE and T-cell NHL with celiac disease and psoriasis. The authors state that the pattern of associations with NHL subtypes might suggest clues to pathogenesis(22); however, there are likely many etiologic factors at play, even within a single type of autoimmune disease.

Regardless, in the general population, chronic immune stimulation has been linked to NHL risk(41), especially in individuals with an underlying genetic predisposition to auto-inflammation. For example, genetic variations in tumor necrosis factor (TNF) alpha expression were shown to influence risk of NHL in a population-based sample(41), where a TNF promoter single-nucleotide polymorphism was clearly associated with diffuse large B-cell lymphoma risk. The authors hypothesized that over-expression of TNF-alpha, by diminishing apoptosis and promoting inflammation via the nuclear transcription factor (NF)-κB pathway, promotes lymphocyte survival and proliferation, thus facilitating lymphoma development. Interleukin (IL) 10 diminishes TNF-alpha production, and the authors of this study also found a heightened NHL risk in individuals with genetic determinants that tend to decrease IL-10 expression.

An alternate explanation is that ongoing exposure to infectious agents drives lymphoma risk, due to the body's chronic inflammatory response. This is an interesting hypothesis, given some evidence that SLE patients may have increased susceptibility to viral infections due to impaired cellular(42) and innate immunity(43). However, the NHL histological types most strongly associated with infectious agents are MALT(44), where helicobacter pylori and hepatitis C have been implicated, and Burkitt's lymphoma, which is clearly associated with EBV(45). Although some autoimmune diseases show a clear tendency towards MALT lymphomas (such as Sjogren's syndrome and Hashimoto's thyroiditis), most of the lymphomas in SLE (as well as RA) are of the diffuse large B-cell type. As a caveat to this, there has been recent evidence suggesting that hepatitis B may play a role in the development of diffuse large B-cell lymphoma, in a Chinese general population sample(46). To date however, there is very little evidence of a strong role for infectious agents as mediators of lymphoma risk in SLE.

Cervical Dysplasia in Women with SLE

The issue of cervical dysplasia remains of considerable importance in SLE. A group of SLE patients with normal cytology tests at baseline was followed to determine the incidence of cervical intraepithelial neoplasia (CIN)(47). The 3-year incidence was 9.8%, significantly higher than figures for the general population. Interestingly, there were no new cases of CIN among SLE subjects exposed only to prednisone or azathioprine; in contrast, in subjects exposed to cyclophosphamide, the incidence of CIN was 15% (4 of 26). Each increase of 1 g of intravenous cyclophosphamide exposure corresponded to a 13% increased risk of CIN incidence.

The major mediator of cervical dysplasia and malignancy is human papilloma virus (HPV) infection. It is therefore of great interest that some SLE patients may have impeded clearance of this virus(48). Tam et al noted that 11 % of Chinese SLE patients w ere infected with high-risk HPV variants (e.g. HPV-16), and this phenomena was not clearly linked to immunosuppressive drug exposures. Similarly, a study from the UK(49) demonstrated HPV-16 in half of the cervical smears from a small (N=30) random sample of SLE patients. Viral DNA measurement showed high viral load in one-third of the SLE subjects where HPV-16 was noted. In that sample, 5 (17%) SLE patients had an abnormal cervical smear and 8 (27%) had intraepithelial lesions. No useful study of the effect of immunosuppressive agents could be performed, given the small sample size. Thus, there is reasonable evidence that women with SLE may have a less effective immune response to HPV, although it is difficult to know how much of the effect is due to baseline immunological abnormalities versus drug exposures. The bottom line appears to be that once SLE patients become sexually active, they should pay attention to cervical cytology screening, as per current guidelines(50). For example, the American College of Obstetricians and Gynecologists recommends yearly cervical cancer screening in immunosuppressed persons, regardless of age, and we would advise yearly pap testing in all women exposed to immunosuppressive therapies (particularly

cyclophosphamide). There is some recent suggestion of disease activity being associated with abnormal cervical cytology in juvenile-onset SLE (51).

Summary

So far, we do know that there is a slight increased risk in SLE for all cancers combined, compared to the general population. However, this is largely driven by an increased risk for hematological malignancies, particularly NHL. Hodgkin's lymphoma may be increased as well. There is a moderately increased risk of lung cancer, and some evidence for increased risk of rarer cancer types, such as hepatobiliarly cancer and vulvar/vaginal malignancies.

There is also very good evidence that cervical dysplasia is increased in women with SLE. This may be mediated by decreased clearance of HPV, which some suggest is an innate characteristic of SLE patients. However, an increased risk of cervical dysplasia is also associated with immunosuppressive medication exposures, particularly cyclophosphamide. Regardless of the source of increased risk for developing cervical dysplasia, it is important that women with SLE follow established guidelines for cervical cancer screening.

Unfortunately, one of the most clinically relevant questions, the mechanism underlying the association between lymphoma and SLE, remains largely unanswered. Recent data suggest that disease-related factors may be at least as important as drug exposures. Work is in progress to further elucidate the relative importance of these two very important, and inter-related, factors.

Practice points

- There is evidence that immune system activity plays a role in the development of some lymphomas, but there is also evidence that immunosuppressive medications can influence the development of certain cancers, and pre-cancerous states such as cervical dysplasia, in autoimmune rheumatic disease populations.
- In many cases, the benefits of immunosuppressive exposures in SLE likely outweigh the relatively small absolute risk of precipitating a malignancy.
- Regarding cervical dysplasia, there is evidence of increased risk related to some medication exposures, particularly cyclophosphamide. Women with SLE should follow the established guidelines for cervical cancer screening.

Research agenda

- Much has been learnt recently regarding the association between cancer and SLE. However, important questions remain regarding the independent influences of medication exposures versus disease activity on lymphoma risk in SLE.
- Establishing which molecular pathways mediate the association between lymphoma and SLE will also be of great value.
- A related research priority is the development of effective SLE treatments that could take the place of toxic agents like cyclophosphamide.

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