The Impact of Autoimmune Diseases on the Incidence and Prognosis of Cutaneous Malignant Melanoma

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Abstract

Background: Persons being treated with IFNα-2b for advanced cutaneous malignant melanoma (CMM) have been reported to have a greatly improved prognosis if they develop autoantibodies or clinical signs of autoimmunity during therapy. Consequently, we examined whether autoimmune diseases might also be associated with lower CMM incidence and better prognosis.

Methods: We established a study cohort based on the entire Danish population, obtaining information on CMM and autoimmune diseases from the Danish national registers. Using log-linear regression models adjusting for age, period, and sex, we compared CMM incidence and CMM-specific mortality rates in persons with and without a history of autoimmune disease.

Results: Between 1977 and 2003, 20,482 cases of CMM were registered in the Danish Cancer Register. Previously diagnosed autoimmune diseases did not affect the incidence of CMM (incidence rate ratio, 1.0; 95% confidence interval, 0.9-1.1). In the first 5 years after CMM diagnosis, we observed 8,957 deaths in individuals with CMM (5,181 expected). CMM-specific mortality rates 1 to 5 years after diagnosis were similar in CMM patients with and without autoimmune diseases (mortality rate ratio, 0.9; 95% confidence interval, 0.7-1.2).

Conclusions: Autoimmune conditions were not associated with CMM incidence or prognosis. The better CMM prognosis previously observed when autoantibodies or clinical signs of autoimmunity developed during IFNα-2b therapy may have been related to variation in individual responses to this therapy, with individuals sensitive to treatment exhibiting more signs of autoimmunity but also (independently) experiencing greater antitumor responses as a result of treatment. (Cancer Epidemiol Biomarkers Prev 2007;16(9):1840–4)

Introduction

Several studies have shown improved overall survival in stages IIIB, IIC, and III cutaneous malignant melanoma (CMM) patients receiving adjuvant therapy with interleukin-2 or high-dose IFNα-2b (1-4). In a recent report, patients in whom autoantibodies or clinical manifestations of autoimmunity developed during treatment with high-dose IFNα-2b were found to have greatly improved survival compared with patients receiving the same therapy who did not develop these autoimmune effects (5). Other small clinical studies have also reported that the development of autoantibodies or clinical signs of autoimmunity during immunomodulating treatment was associated with better-than-expected CMM prognosis; examples include the development of vitiligo (6), hypothyroidism (7-10), autoimmune retinopathy (11), and the antiphospholipids syndrome (12). The mechanisms by which autoimmunity responses might lead to better antitumor efficacy were speculated to involve immune surveillance. Autoimmune conditions are thought to reflect greater immunologic reactivity and, therefore, perhaps enhanced immune surveillance for cancer cells. However, there are other possible mechanisms that would explain the association between IFN-induced autoimmune conditions and better CMM prognosis more trivially. For example, high levels of lysis in IFN-sensitive tumors could produce large amounts of cell antigens and thereby trigger autoantibody development (13). Alternatively, there may be individual variation in the metabolism of IFN, with poor degradation leading to both better prognosis and, independently, more autoimmune or autoantibody outcomes. It remains unclear whether the observed better CMM prognosis is related to autoimmunity itself or to a greater sensitivity to treatments that also result in autoimmune responses.

Materials and Methods

Data Sources. The Danish Civil Registration System (CRS) has assigned a unique personal identification number to each resident of Denmark since April 1, 1968 (14). The CRS records demographic information for each individual, including name, gender, date and place...
of birth, and citizenship. It also tracks vital status and emigration from Denmark, providing the date of death, disappearance, or emigration. The personal identification number also permits accurate linkage of individual-level information in Denmark’s national registers.

We obtained information about CMM from the Danish Cancer Register, which has registered incident cases of cancer diagnosed in Denmark since 1943 and is considered close to complete (15). A person was considered to have CMM on the first date such a diagnosis was noted in the Cancer Register [International Classification of Diseases (ICD), 7th Revision, code 190].

Information on autoimmune diseases was obtained from the Danish National Patient Register, which has recorded information on all hospitalizations in Denmark since 1977 and all outpatient hospital and consultant visits since 1995. Diagnoses (discharge diagnoses for inpatients) were registered using ICD-8 codes between 1977 and 1993 and ICD-10 codes thereafter. Lists of autoimmune conditions differ from reference to reference. We included as autoimmune diseases the 44 conditions defined and classified as such in Harrison’s Principles of Internal Medicine (16, 17), along with Dupytren’s disease, amyotrophic lateral sclerosis, and induratio penis plastica.4 Despite differences in the ICD-8 and ICD-10 coding schemes, major categories of autoimmune conditions could consistently be recognized and grouped.

**Definition of Cohorts and Statistical Methods.** We examined the risk of developing CMM in persons with and without autoimmune disease using a cohort of all persons alive and living in Denmark in 1977 or born in Denmark thereafter. Follow-up started on January 1, 1977, or a person’s 15th birthday, whichever came later. The risk period for developing CMM continued until the first date any autoimmune disease was registered in the National Patient Register. The association between a history of autoimmune disease and CMM was expressed using incidence rate ratios (IRR) estimated from a log-linear Poisson regression model; we modeled the logarithm of person-years at risk as the offset. IRR estimates were adjusted for attained age (1-year categories), calendar period (1-year categories), and sex. A history of autoimmune disease was defined as described above; an autoimmune disease diagnosis was considered to persons with two or more registrations of the same autoimmune disease and repeated our analyses.

Estimation was done using the SAS procedure PROC GENMOD (version 9.1).

We examined CMM prognosis in persons with and without an autoimmune disease using a cohort of all persons diagnosed with CMM between January 1, 1977, and December 31, 2003, identified through the Danish Cancer Register. A history of autoimmune disease was defined as described above; an autoimmune disease diagnosis could come before or after CMM diagnosis. Follow-up started at the time of CMM diagnosis and continued for 5 years or until death, emigration, or December 31, 2003, whichever came first. The association between a history of autoimmune disease and CMM prognosis was evaluated in a Poisson regression model with observed number of deaths as the outcome and the logarithm of person-years at risk as the offset. Covariates in the model included history of autoimmune disease, attained age (1-year categories), calendar period (1-year categories), and sex. We used the link function \( \log(L - E) \), where \( L \) is the linear sum of covariates \( \Sigma(\beta X) \) and \( E \) is the expected number of deaths according to attained age, calendar period, sex, and history of autoimmune disease (history/no history). (The expected number of deaths was estimated using a model of national death rates in persons without CMM, adjusting for attained age, calendar period, sex, and history of autoimmune disease and including an interaction between age and history of autoimmune disease). By introducing this alternative link, the CMM prognosis model can be viewed as a log-linear model of the observed death rate in CMM patients minus the expected death rate; in other words, this approach

### Table 1. Adjusted IRRs for CMM by years since autoimmune disease diagnosis

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 y</th>
<th>≥1 y</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CMM cases</td>
<td>Person-years</td>
<td>IRR 95% CI</td>
<td>CMM Cases</td>
</tr>
<tr>
<td>Diabetes</td>
<td>72</td>
<td>213</td>
<td>1.3 (1.0-1.6)</td>
<td>345</td>
</tr>
<tr>
<td>Non-diabetes autoimmune diseases</td>
<td>66</td>
<td>236</td>
<td>1.3 (1.0-1.6)</td>
<td>524</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>15</td>
<td>28</td>
<td>1.5 (0.9-2.6)</td>
<td>57</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>4</td>
<td>5</td>
<td>3.7 (1.4-9.9)</td>
<td>11</td>
</tr>
<tr>
<td>Systemic sclerosis (scleroderma)</td>
<td>1</td>
<td>2</td>
<td>1.7 (0.2-12.3)</td>
<td>6</td>
</tr>
<tr>
<td>Erythema nodosa</td>
<td>0</td>
<td>3</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>All autoimmune diseases</td>
<td>132</td>
<td>431</td>
<td>1.3 (1.1-1.5)</td>
<td>843</td>
</tr>
</tbody>
</table>

NOTE: Adjusted for age, calendar period, and sex.

*Cutaneous malignant melanoma cases. Case numbers in the individual categories do not add up to the number of cases for all autoimmune diseases because a few persons had more than one autoimmune disease.

1 Person-years in thousands.
modeled the excess mortality due to CMM. Consequently, the estimated rate ratios were interpreted as ratios of CMM-specific mortality rates and are termed mortality rate ratios (MRR).

Results

Overall, 20,482 CMM cases were observed during 150,964,190 person-years of follow-up. Observed associations between selected autoimmune diseases and CMM incidence are shown in Table 1. Persons diagnosed with any autoimmune disease had a 30% [95% confidence interval (95% CI), 10-50%] higher incidence of CMM within 1 year of autoimmune disease diagnosis than persons without an autoimmune disease. This finding was observed in both persons with diabetes (the most common single autoimmune condition) and those with other autoimmune diseases. In contrast, excluding the first year after diagnosis of an autoimmune disease of any type, CMM incidence was similar in persons with and without autoimmune diseases (Table 1; IRR, 1.0; 95% CI, 0.9-1.1).

Among persons with CMM, 8,957 died within 5 years of diagnosis. Of these, 5,181 deaths were expected due to other causes (based on national death rate information), leaving 3,776 excess deaths attributable to CMM. When autoimmune diseases and CMM were diagnosed within 1 year of one another, CMM mortality in patients with diabetes was higher than expected (MRR, 3.5; 95% CI, 2.2-5.5), whereas for other autoimmune diseases, there was no increase in mortality (MRR, 1.0; 95% CI, 0.4-2.6; Table 2). Excluding those patients in whom CMM and autoimmune conditions were diagnosed within 1 year of one another, there was no excess mortality from CMM within 5 years of the CMM diagnosis in persons with an autoimmune disease, compared with those without (MRR, 0.9; 95% CI, 0.7-1.2). This was the case for both diabetes (MRR, 1.0; 95% CI, 0.7-1.5) and other autoimmune diseases (MRR, 0.9; 95% CI, 0.7-1.3).

Excluding persons diagnosed with both CMM and diabetes within a 1-year period and limiting analyses to persons registered at least twice with a diabetes diagnosis, there was no evidence of any effect of diabetes on CMM incidence (IRR, 0.9; 95% CI, 0.8-1.0) or prognosis (MRR, 1.1; 95% CI, 0.6-2.0). Similarly restricted analyses for the non-diabetes autoimmune diseases also showed no effect of these autoimmune diseases on CMM incidence (IRR, 1.0; 95% CI, 0.9-1.1) or prognosis (MRR, 1.0; 95% CI, 0.5-1.7). Small numbers precluded similar analyses of the effect of autoimmune diseases diagnosed within 1 year of CMM.

Discussion

To our knowledge, only one study of the association between autoimmune disease and the incidence of CMM has previously been reported; in this study, which examined cancer risk in persons diagnosed with rheumatoid arthritis, no significant association between rheumatoid arthritis and CMM incidence was found (18). No studies have related autoimmune disease and CMM prognosis. We observed a significant 30% increase in CMM incidence in persons with a new autoimmune disease diagnosis (within 1 year of CMM diagnosis), compared with persons without a history of autoimmune disease, but no difference in CMM incidence in persons whose autoimmune diseases had been diagnosed more than 1 year before their CMM diagnoses. Persons with newly diagnosed autoimmune diseases also had significantly worse CMM prognoses than those without autoimmune disease; this excess mortality was solely attributable to the 3.5-fold excess mortality observed in patients with diabetes. For persons whose CMM and autoimmune disease diagnoses were separated by more than 1 year, there was no excess mortality associated with either diabetes or other autoimmune diseases. Thus, the impact of autoimmune diseases on CMM incidence and prognosis was limited to autoimmune diseases diagnosed within 1 year of CMM diagnosis.

Our interest in examining the relationship between autoimmune diseases and CMM was provoked by a recent report suggesting that persons developing autoantibodies or clinical symptoms of an autoimmune disease during IFN-α2b therapy had a considerably better prognosis than those who did not develop such signs and symptoms (5). The authors ascribed this effect to immune activation by IFN. We reasoned that if this rationale was correct, it ought also to apply to persons developing autoimmune conditions naturally. However, our data suggest that having an autoimmune disease does not improve CMM prognosis. Although poorer CMM prognosis could be expected in persons...
with autoimmune diseases because of the comorbidity inherent in having two serious conditions, we examined excess mortality beyond that expected to be due to autoimmune diseases alone, thereby comparing CMM-specific mortality in persons with and without autoimmune diseases. Despite this rigor, we observed no beneficial effect associated with having an autoimmune disease.

This lack of effect might have been caused by breakthrough disease, in which CMM occurring in persons with an autoimmune disease was resistant to the putative effects of immune activation. If immunosurveillance from an immune system activated by an autoimmune disease was effective in preventing CMM, the incidence of CMM would be expected to be lower in persons with autoimmune diseases. However, the incidence of CMM in persons with autoimmune diseases was in fact significantly higher within 1 year of autoimmune disease diagnosis than the incidence in persons without autoimmune diseases. We attribute this increased incidence to increased medical attention around the time of initial autoimmune disease evaluation. Excluding the first year after autoimmune disease diagnosis, the incidence of CMM in persons with autoimmune diseases was similar to that in persons without autoimmune diseases.

Because we did not find any association between autoimmune disease and CMM incidence or prognosis, our study does not support the hypothesis that autoimmunity itself is associated with improved CMM survival. An alternative explanation for the findings of improved survival in persons developing autoimmune signs and symptoms after IFNα-2b treatment may be that IFN sensitivity and metabolism vary between individuals. IFNα-2b is well known to cause autoimmune effects at high doses (19). Therefore, patients who are more sensitive to IFNα-2b or who metabolize it more slowly may simply have more autoimmune problems than less sensitive individuals, but may also benefit more from treatment (i.e., may exhibit a more active antitumor response), independent of their autoimmune response.

When autoimmune disease and CMM diagnoses occurred within 1 year of one another, we observed much worse CMM prognosis in persons with diabetes compared with persons with other autoimmune diseases. This may have occurred because late-stage CMM patients, who are at high risk of dying, are often treated with glucocorticoid therapy, a treatment known to induce diabetes in previously nondiabetic persons as well as to aggravate existing diabetes (20).

Our observations are unlikely to be attributable to bias. We conducted a follow-up study on a large, population-based cohort, making selection bias unlikely. Furthermore, there are no obvious common risk factors for autoimmune diseases and CMM, making confounding improbable. Registration of cancer, including CMM, has been mandatory in Denmark since 1943 and is considered close to complete (15). Regarding the registration and validity of autoimmune disease diagnoses, three points should be noted. First, data on autoimmune diseases were obtained from the Danish National Patient Register, which has registered inpatient diagnoses since 1977 and outpatient/clinic diagnoses since 1995. Thus, autoimmune conditions diagnosed before 1997 or diagnosed in an outpatient setting in the period 1977 to 1994 were missed if they were not also registered at a later date. However, due to the rarity of autoimmune diseases, later or missed registrations would result in only a small number of misclassified person-years in the large group with no history of autoimmune disease. Second, diagnosing an autoimmune disease can be difficult, and registries of a single autoimmune disease diagnosis may not necessarily represent a confirmed diagnosis (21). To ensure the validity of our autoimmune disease diagnoses, we restricted the definition of persons with autoimmune disease to persons with two or more registrations of the same autoimmune disease diagnosis and repeated our analyses. This more conservative approach yielded similar results to those seen using the broader definition. Third, the National Patient Register only records disease diagnosed or treated in hospitals and outpatient/specialty clinics and does not register diagnoses made by general practitioners. However, our study only included the more severe autoimmune diseases, which require contact with a hospital or consultant at some point in their course, and for which registration was therefore likely to be fairly complete.

In conclusion, when we examined autoimmune disease and CMM diagnoses separated by more than 1 year, we found no association between autoimmune diseases and either incidence or prognosis of CMM. The increased incidence of CMM within 1 year of autoimmune disease diagnosis may have been affected by bias in the ascertainment of CMM. For individuals diagnosed with diabetes within 1 year of CMM diagnosis, CMM therapies may have adversely affected diabetes management and thereby prognosis. Overall, our findings do not support the hypothesis that autoimmunity itself affects CMM incidence or prognosis. Rather, the results suggest that the reported relationship between autoimmunity and CMM prognosis may be a result of individual variations in sensitivity to or metabolism of IFNα-2b or other immunomodulating treatments in CMM patients.

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References

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