Cancer preceding Wegener’s granulomatosis: a case–control study

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Objective. To investigate whether patients with WG have an increased risk of malignancies prior to and/or around the time of the vasculitis diagnosis, as suggested by previous studies.

Methods. A total of 293 WG patients were included in the study. Ten gender- and age-matched controls were selected randomly for each patient from the Danish Central Population Register. Information on malignancies was obtained through the Danish Cancer Registry. Occurrence of malignancies before WG diagnosis among patients and before WG diagnosis of their matched case among controls (reference date) was compared by calculation of prevalence odds ratios (OR).

Results. Twenty-six patients were diagnosed with cancer before WG, while 194 controls were diagnosed with cancer before the reference date (OR 1.4; 95% CI 0.9, 2.2). Among specific malignancies, a significantly increased prevalence was found for testis cancer (OR 6.4; 95% CI 1.1, 38) based on two patients, who developed testis cancer >10 years before WG. The overall prevalence of malignancies diagnosed <2 years before WG was not significantly increased (OR: 1.6; 95% CI: 0.8, 3.4), but non-melanoma skin cancer occurred with an increased prevalence within this time interval (OR 4.0; 95% CI 1.4, 12).

Conclusions. We did not find clear evidence of an increased prevalence of preceding cancer in our WG cohort, indicating that shared risk factors are of minor importance for the excess of malignancies that occur in WG patients after the vasculitis diagnosis. Furthermore, our current and previously reported latency analyses do not substantiate that serious malignancies play a significant role in the pathogenic events that trigger development of WG.

Key words: Wegener’s granulomatosis, Vasculitis, Cancer, Malignancy, Non-melanoma skin cancer, Case–control study.

Introduction

WG is a systemic disorder of unknown aetiology characterized by granulomatous inflammation, necrotising vasculitis in small- to medium-sized blood vessels and the presence of circulating ANCA. The disease involves the respiratory tract and the kidneys in the majority of patients, but any organ system can be affected [1–4]. WG is distinguished from other ANCA-associated vasculitides, i.e. microscopic polyangiitis and Churg–Strauss syndrome, on the basis of clinical, histological and serological criteria [1, 3, 4]. Standard treatment for induction of remission in WG consists of therapy with cyclophosphamide (CYC) and corticosteroids [2, 5–8]. Due to the carcinogenic potential of CYC, treatment with this agent is associated with a substantial risk of late-occurring malignancies. Several studies have demonstrated an increased incidence of cancer among WG patients treated with CYC [2, 9–12], and the risk of cancer correlates with the cumulative CYC dose received [9, 13]. Intriguingly, epidemiological studies indicate that the occurrence of malignancies might be increased among WG patients even before the onset and treatment of vasculitis [13–15]. Thus, Tatsis and co-workers [14] compared the prevalence of preceding malignancies in a cohort of 477 WG patients with the corresponding prevalence among 479 patients with RA. In this study, a significantly increased odds ratio (OR) was found for renal cell carcinoma and for simultaneous occurrence of cancer and vasculitis in the WG group. Knight et al. [13] reported that a history of bladder cancer was non-significantly twice as common as expected at the time of vasculitis diagnosis among 1065 WG patients. Recently, Pankhurst et al. [15] found a significantly increased rate of malignancies predating the debut of vasculitis in a cohort of 200 patients with ANCA-associated vasculitides when compared with the cancer rate in a sex- and age-matched control group. However, no separate risk estimates were given for the 78 WG patients in the cohort [15]. These findings have led to suggestions that WG might be somehow linked to malignancy at the pathogenic level [14, 16]. Furthermore, it has been proposed that malignancy should be considered a potential differential diagnosis in patients presenting with ANCA-associated vasculitis [15] and that patients with newly diagnosed WG should be screened for the presence of underlying cancer [14, 16].

The Danish Cancer Registry contains information on all malignancies diagnosed in Denmark and consequently provides a unique opportunity for epidemiological studies of cancer [17]. In order to investigate further whether WG is associated with an increased prevalence of preceding cancer, we designed a retrospective case-control study involving 293 WG patients, each matched with 10 population controls.

Patients and methods

Patients and controls

The WG cohort was established as previously described [9]. The Danish National Hospital Register was used to identify patients discharged from Danish hospitals with a diagnosis of WG. This Register was established in 1977 and contains information on >99% of all admissions to non-psychiatric hospital departments in Denmark [18]. Since 1 January 1994, inpatient registration has been supplemented by information on outpatient hospital visits. Each hospital contact initiates a record, which is coded by the patient’s personal identification number and includes the dates of admission and discharge, start and end dates of outpatient visits, a primary diagnosis diagnosis and supplementary diagnoses. The diagnoses were coded according to a Danish version of the International Classification of Diseases, 8th Revision (ICD-8) until the end of 1993 and according to the 10th Revision (ICD-10) thereafter. A search was performed for the medical records of
all patients registered in the Danish National Hospital Register with a diagnosis of WG (ICD-8: 446.29; ICD-10: M31.3) during the period 1977-99. Available medical files were reviewed, and patients who retrospectively met the ACR classification criteria for WG [1] were included in the study on the condition that they were living in Denmark at the time of the vasculitis diagnosis. Patients whose medical files were missing or incomplete were excluded from further analyses. With this approach, we identified 293 patients diagnosed with WG in Denmark between 1973 and 1999. For each WG patient, 10 population controls were chosen at random from the Danish Central Population Register, which contains key information on all citizens of Denmark, including dates of death and emigration. Controls were matched to the case on gender and exact year of birth and were eligible if they were alive and living in Denmark on the date of the WG diagnosis of their matched case. Information on malignancies was obtained by linkage to the Danish Cancer Registry, which has collected data on cancers diagnosed in Denmark since 1943 and has almost complete coverage [17]. Most of the malignancies in the Registry are verified by histology (84.3% during the period 1943-92), but malignancies verified by other methods are also accepted and included [17]. Malignancies are coded according to the Danish version of the ICD, Seventh Revision (ICD-7) [19] and, since 1978, according to the ICD for Oncology (ICD-O-1) [20].

**Statistics**

The occurrence of malignancies prior to the diagnosis of WG among cases was compared with the occurrence of malignancies prior to a reference date among controls. The reference date for the controls was defined as the date of WG diagnosis of their matched case. The association between cancer and WG was expressed as a prevalence OR computed by conditional logistic regression for matched sets [21]. The degree of statistical impression was expressed by the 95% CI around the risk estimate. We calculated ORs for prior cancers at all sites combined and for specific cancer sites. If a person had more than one cancer diagnosis, each diagnosis was counted in the relevant category. In addition, we calculated ORs for two intervals between the date of cancer diagnosis and the date of WG diagnosis (<2 years and ≥2 years), and for two age groups of WG patients (<50 years and ≥50 years at the date of WG diagnosis). In all analyses, we chose ‘no previous cancer’ as the reference level. The conditional logistic regression analyses were carried out with the SAS procedure PHREG (SAS version 8 by SAS Institute Inc., Cary, NC, USA).

**Results**

Basic descriptive data of patients and controls are summarized in Table 1. The median age of the patients at the time of WG diagnosis was 59 years (range 14-88 years). In the WG group, a total of 26 malignancies occurred in 26 patients prior to the diagnosis of vasculitis, while 208 malignancies occurred in 194 subjects before the reference date in the control group. Prevalence ORs for cancer at all sites combined and for specific types of cancer are shown in Table 2. The OR for a prior cancer at any site was not significantly increased. Among specific malignancies, a significantly increased prevalence was found for testis cancer on the basis of two WG patients, in whom this cancer was diagnosed 10.8 and 19.6 years before WG, respectively. An increased prevalence was also found for malignancies listed as kidney cancers. However, two of the three kidney cancers were renal cell carcinomas for which a non-significantly elevated prevalence was seen, while the third case of kidney cancer was a papillary transitional cell carcinoma of the renal pelvis. These malignancies occurred 3.2 years (renal cell carcinoma), 3.5 years (papillary transitional cell carcinoma) and 9.7 years (renal cell carcinoma) before WG.

Table 3 shows the ORs for malignancies at selected sites in analyses stratified according to time between cancer and WG. The overall prevalence of cancer diagnosed <2 years before WG was not significantly increased. However, non-melanoma skin cancer occurred with a 4-fold, significantly increased prevalence within this interval. The five cases of non-melanoma skin cancer diagnosed <2 years before WG comprised two cases of squamous cell carcinoma and three cases of basal cell carcinoma, which predated WG by 7–14 months.

In analyses stratified according to age, no increase in cancer prevalence was found for either young WG patients (OR for cancer at any site for patients <50 years at date of WG diagnosis: 1.0; 95% CI 0.1, 7.8; number of cases with cancer = 1, number of controls with cancer = 10) or elderly patients (OR for cancer at any site for patients ≥50 years at date of WG diagnosis: 1.4; 95% CI 0.9, 2.3; number of cases with cancer = 25, number of controls with cancer = 184).

**Discussion**

Compared with age- and gender-matched controls, the WG patients of the present study did not experience a significantly...
increased overall number of malignancies prior to the vasculitis diagnosis. The prevalence of preceding testis cancer was significantly increased, but this finding was based on only two WG patients, who developed testis cancer >10 years before WG.

We recently investigated the incidence of malignancies occurring after the WG diagnosis in the same group of patients as described in the present study [9]. For patients treated with CYC, the incidence of malignancies was found to be significantly increased compared with the cancer incidence in the Danish background population, and high risks of bladder cancer and acute myeloid leukaemia were found for patients treated with a cumulative CYC dose of >36 g (corresponding to therapy with 100 mg CYC daily for ~1 year). The incidence of malignancies was not, however, increased in the cohort during the first year following the WG diagnosis, and no specific malignancies occurred at increased incidence during this time interval. In the present study, only non-melanoma skin cancers were diagnosed with an increased prevalence <2 years before the WG diagnosis. Thus, the combined latency analyses of our recently published follow-up study [9] and the current case-control study do not confirm the strong association between simultaneous occurrence of serious malignancies and WG described by others [14]. With regard to renal cell carcinoma, we did not detect a single case occurring <3.2 years before WG in the present study, and no patients were diagnosed with renal cell carcinoma during the first year after the WG diagnosis [9]. Like Pankhurst et al. [15], we are therefore unable to confirm the previously reported temporal association between this type of cancer and WG [14]. Furthermore, our analyses do not substantiate the hypothesis that the occurrence of bladder cancer might be increased among WG patients even before the diagnosis of WG and treatment with CYC [13].

The present study shows a 4-fold increase in the prevalence of non-melanoma skin cancers occurring <2 years before the diagnosis of vasculitis in the WG group. Obviously, a potential methodological explanation is surveillance bias. To this end, it could be hypothesised that an increased number of non-melanoma skin cancers was detected during the diagnostic programme leading to the WG diagnosis. However, the fact that no cases of non-melanoma skin cancer were diagnosed <7 months before WG or within the first year after the WG diagnosis [9] strongly argues against this possibility. Due to the low propensity for invasive growth and the relatively benign nature of non-melanoma skin cancers, it seems implausible that vasculitis developed as a para-neoplastic syndrome in the five patients diagnosed with these malignancies <2 years before WG. The well-established association between immunosuppression and development of non-melanoma skin cancer [22–24] makes it more tempting to speculate that the observed temporal relationship between non-melanoma skin cancer and subsequent WG reflects a state of acquired immunological dysfunction that predisposes to both conditions.

This study is the first systematic investigation of the prevalence of all types of cancer occurring before the vasculitis diagnosis among WG patients. The high-quality data of the Danish Cancer Registry allowed us to calculate prevalence ORs for different malignancies in analyses stratified according to time between cancer and WG. Additional strengths of the study include a high validity of the WG diagnoses, a relatively large cohort of WG patients, unbiased selection of controls by use of a national population register, and unbiased data on cancer diagnoses. Our study also has methodological weaknesses. In light of the demographic development in Denmark during the period of study, ~5% of cases and controls could potentially have been immigrants, and any cancer diagnosis occurring before immigration might not have been recorded in the Danish Cancer Registry; however, the number of cancer diagnoses missed is likely to be limited. As we investigated multiple associations between WG and preceding cancer, the few statistically significant findings, e.g. for testis cancer, could be the result of chance. Moreover, risk-estimates for several malignancy types are based on a small number of cancer cases and therefore have wide CIs. The limited number of malignancies also implies the risk of a statistical type II error, i.e. the risk of overlooking a real association between WG and prior cancer. Finally, the WG patients were identified from the Danish National Hospital Register, whereas the exact dates of the WG diagnoses were obtained from the medical files of the patients. For most cases, the registration date in the National Hospital Register and the date of WG diagnosis were closely related in time, and only a few patients were diagnosed with WG before registrations in the National Hospital Register began in 1977 (n = 4). A potential survival bias, which could theoretically be in the direction to underestimate the prevalence of preceding cancer in the WG group, is therefore expected to have a very low impact on the prevalence estimates.

In conclusion, we did not find clear evidence of an increased prevalence of preceding cancer in our WG cohort, suggesting that shared risk factors for cancer and WG are of minor importance for the excess of malignancies that occur in WG patients after the diagnosis of vasculitis. Furthermore, the latency analyses of the present investigation and those of our previously published
follow-up study of the same group of WG patients [9] do not substantiate that malignancies play a significant role in the pathogenic events which trigger the development of WG. Thus, from a clinical perspective, our data do not support that patients with newly diagnosed WG should be routinely examined for the presence of underlying, serious malignancy.

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References