Concise Report

Risk of cancer in patients with biopsy-proven giant cell arteritis

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Abstract

Objective. Results of previous studies investigating the association between GCA and malignancy are conflicting. We performed a study of the risk of cancer in patients with biopsy-proven GCA.

Methods. Patients with biopsy-proven GCA were identified from pathology reports of temporal artery biopsies from the major pathology laboratories in South Australia (SA). All subjects with biopsy-proven GCA were linked to the SA Cancer Registry to identify cases of cancer until 31 December 2006. Standardized incidence ratios (SIRs) for cancer were determined using the age- and gender-specific rates for SA.

Results. There were 226 cases of biopsy-proven GCA (163 females and 63 males). Thirty-one cases were diagnosed with cancer, following the diagnosis of biopsy-proven GCA. There was no increased risk of cancer among those with biopsy-proven GCA, following the diagnosis of GCA compared with the general population (SIR 1.2; 95% CI 0.8, 1.6).

Conclusion. This cohort study did not demonstrate any increased risk for malignancy in subjects with biopsy-proven GCA.

Key words: Giant cell arteritis, Malignancy, Epidemiology, Population.

Introduction

There have been numerous case reports and case series of patients with co-existing GCA and malignancy, raising the possibility that, in some patients, GCA may represent a paraneoplastic phenomenon similar to DM. Recently, Liozin and colleagues [1] published a case series of 20 patients with concurrent GCA and malignancy; with the mean time between diagnosis of GCA and malignancy of 3.5 months, with various types of malignancy reported in this study. However, epidemiological studies demonstrate conflicting results with regard to the association of GCA with malignancy. Two Norwegian studies [2, 3] demonstrated no increased risk of malignancy in patients with GCA or PMR. However, one of these studies did demonstrate an increased risk of malignancy in a subset of 65 patients with biopsy-proven GCA [2]. Most recently, a study of patients with biopsy-proven GCA from a single centre in Spain demonstrated no increase in cancer-related mortality compared with the general Spanish population [4]. The objective of this study was to determine the association between cancer and biopsy-proven GCA in the South Australian population.

Methods

Ascertainment of biopsy-proven GCA cases

All pathology reports of patients who underwent temporal artery biopsy were identified from pathology laboratories at the three major South Australian adult teaching hospitals (The Queen Elizabeth Hospital, Royal Adelaide Hospital and Flinders Medical Centre). These laboratories process pathological biopsy specimens for both public and private hospitals for ~85% of the South Australia (SA). Temporal artery biopsies were identified at the Queen Elizabeth Hospital in the time period 1 January 1991 to 31 December 2006, Royal Adelaide Hospital...
1 January 1991 to 31 December 2006 and Flinders Medical Centre 1 January 1995 to 31 December 2006. The pathology reports were reviewed to identify patients with biopsy-proven GCA. Patients were defined as having biopsy-proven GCA if this diagnosis was made by the reviewing pathologist on the diagnostic report.

Cancer ascertainment

The South Australian Cancer Registry has notification of cancer in SA [5], from pathology laboratories, medical record departments of hospitals, radiotherapy departments and oncologists. The registry of births, deaths and marriages also provides details of deaths affecting all people notified to the cancer registry, irrespective of cause of death, as well as to the general SA population. Non-melanoma skin cancers are not included in the registry. Cancer cases on the SA Cancer Registry are checked for completeness by multiple electronic searches of each year’s records of all South Australian pathology and haematology laboratories and public and private hospitals. In addition, the International Agency for Research on Cancer also checks the quality of the South Australian Registry data every 5 years. Using Automatch software (Matchware Technologies, Tampa, USA), all patients identified with biopsy-proven GCA were linked to the South Australian Cancer Registry to identify all cases of cancer among these subjects before 1 January 2007. In addition, there was linkage to the Registry of Birth, Deaths and Marriages to identify patients who had died (from cancer or any other cause) during follow-up until 1 January 2007. Analyses were undertaken at the Cancer Registry such that the release of identified data on cancer cases was not required.

Analysis

A historic cohort analysis was undertaken, using STATA 6.0 software (STATA Corporation, College Station, TX, USA). Patients with biopsy-proven GCA were followed from their date of temporal artery biopsy until either their death or 31 December 2006, whichever came first. Each month of follow-up was classified by calendar year and by sex of patients and age at that time.

To determine the risk of cancer in patients with biopsy-proven GCA after the diagnosis of GCA, the number of cancers expected in this cohort was calculated by applying cancer incidence rates for SA, classified by calendar year, age and sex, to these months of follow-up. The risk of cancer in the general South Australian population was compared with the patients with biopsy-proven GCA.

Standardized incidence ratios (SIRs) were obtained indirectly by dividing the numbers of cancers observed with the numbers expected, and deriving 95% CI of these ratios from the Poisson distribution. The SIRs use the general SA population as the referent group. Therefore, by definition, this group will have an SIR of 1.0.

Analyses were undertaken for all cancer sites collectively and for individual sites [using International Classification of Diseases (ICD)-9 codes] where numbers were sufficient.

Cancers diagnosed before the diagnosis of biopsy-proven GCA were identified and classified according to the cancer site (using ICD-9 codes) and by the number of years before the diagnosis of biopsy-proven GCA. These cancers were not included in the analysis described above.

The study was approved by the Human Ethics Committees of the Royal Adelaide Hospital, North West Adelaide Health Service, Flinders Medical Centre and South Australian Department of Health.

Results

We identified 226 positive temporal artery biopsies, of which 163 (72.2%) were females. The mean age was 75.5 (S.D. 8.0) years with a median follow-up of 44.6 months. At the time of censoring on 31 December 2006, 89 (39.3%) patients had died. Fifty-six (24.6%) patients had been diagnosed with cancer. Of these, 25 had a cancer diagnosis before GCA diagnosis. Five patients had multiple diagnoses of cancer. Three patients had cancers diagnosed both before and after diagnosis with GCA, one case had two cancers diagnosed after GCA diagnosis, and one case had two cancers diagnosed before GCA diagnosis. There was no difference in the age of the GCA patients with or without cancer ($P = 0.72$).

There were 25 patients who had cancer diagnosed before GCA diagnosis. These included breast (in seven patients), lung (three), colorectal (three), uterus (two), prostate (two), malignant melanoma (two), bladder (two), cervix (one), lip (one), multiple myeloma (one), gum (one), heart (one) and renal (one) cancers.

For the 31 patients with cancer diagnosed following GCA diagnosis, the median time to cancer diagnosis was 39.5 (interquartile range 60.1) months. There were five cases where cancer occurred either at the time or within 3 months after the GCA diagnosis. The risk of cancer in patients with biopsy-proven GCA following the diagnosis was not increased with SIR for all cancers was not raised, nor was there any difference between males or females (Table 1). When we studied individual cancer risks, the only significantly elevated SIR was prostate cancer (SIR 2.4). However, this increased risk was only marginally statistically significant ($P = 0.04$) and we could not conclude that there was no increased risk of prostate cancer.

Discussion

This study of biopsy-proven GCA did not demonstrate an increased risk of malignancy. The strengths of our study include the high quality of the SA Cancer Registry and the near full ascertainment of biopsy-proven GCA cases in SA. There did appear to be some sex differences in the diagnosis of cancer following GCA diagnosis; however, again, this may be related to surveillance as men are less likely to be involved in cancer screening programmes than women [6]. A limitation was the lack of clinical data from the patients with biopsy-proven GCA and the exclusion of patients with biopsy-negative GCA.
A recent case series of 271 consecutive patients with GCA (219 biopsy-proven) found 20 (7.4%) patients with concurrent cancer, suggesting that there was a temporal association between malignancy and diagnosis of GCA [1]. Of these concurrent malignancies, there were 12 solid tumours, 6 myelodysplastic syndromes and 2 chronic leukaemias. Many of these malignancies have long latencies and diagnosis around the time of GCA may be related to increased surveillance. They found no clinical differences in GCA between those patients with and without cancer.

Two previous epidemiological studies from Norway have been undertaken. Haga et al. [2] studied 185 patients diagnosed with PMR or GCA at two Bergen hospitals during a 5-year period from 1978. These were matched with 925 population controls and were subsequently linked to the Norwegian Cancer Registry. This study found no association between malignancy and cancer in patients with PMR or GCA. However, in a subset of 65 patients with biopsy-proven GCA, 16 (24.6%) were diagnosed with cancer with an increased risk of malignancy compared with the general population (hazard ratio 2.35; 95% CI 1.03, 13.24; P = 0.007). They generally found a long interval between GCA diagnosis and cancer. A prospective population-based study from Aust Agder County in Norway in which 398 patients with PMR or GCA were compared with four age- and sex-matched population controls (1592 controls) found no increased risk of cancer in patients with PMR or GCA compared with the general population [3]. In the subset of 80 patients with biopsy-proven GCA, there was no statistically significant increased risk of cancer, compared with controls (SIR 1.48; 95% CI 0.65, 3.4). Most recently, Gonzalez-Gay et al. [4] studied 255 patients with biopsy-proven GCA in a single centre in northwest Spain. Cancers and cancer-related mortality was ascertained from casenote review. The standardized mortality ratio (SMR) from cancer was calculated using Spanish national cancer mortality data. This demonstrated no increased risk of dying from cancer compared with the general population (SMR 1.06; 95% CI 0.65, 1.60). Eighteen per cent (7/39) of the cancers were diagnosed within the first 12 months of GCA diagnosis, with the frequency of concurrent GCA and malignancy within the first 12 months after GCA diagnosis being 2.75%. Extensive clinical data were collected in this study on patients with biopsy-proven GCA. The presence of dysphagia, abnormal temporal artery on physical examination and anaemia at the time of GCA diagnosis were associated with an increased risk of cancer over the extended follow-up period after multivariate analysis. These data did not support an increased risk of dying from cancer in patients with biopsy-proven data. However, it is likely that there was an incomplete ascertainment of cancers and no comparison for population cancer incidence was available.

Our study has important advantages over previous studies, as we were able to ascertain cases of biopsy-proven GCA from the general population and linked it to the SA Cancer Registry, which has near complete ascertainment.
of cancers in SA. However, the current study had limited power to detect an increased risk of cancer in specific cancer sites. In conclusion, this study demonstrated no increased risk of malignancy in patients with biopsy-proven GCA.

**Rheumatology key message**
- We did not find evidence of an association between cancer and biopsy-proven GCA in this population.

**Acknowledgements**

We thank Ann-Marie Twisk and Colin Luke of South Australian Cancer Registry for their help with this study.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**