Cancer development in Korean patients with ANCA-associated vasculitis: a single centre study

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ABSTRACT

Objectives. *We investigated the incidence rate and type of cancer, and furthermore, estimated the standardised incidence ratios (SIRs) of cancer in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in Korea.*

Methods. *We retrospectively included 150 patients with AAV [81 patients with microscopic polyangiitis (MPA), 38 with granulomatosis with polyangiitis (GPA) and 31 patients with eosinophilic GPA (EGPA)], and reviewed their medical records. We collected demographic, clinical and laboratory data, and reviewed the use of glucocorticoid and immunosuppressive drugs administered until detection of cancer or last visit. We estimated the SIRs of cancer according to totality, gender, age, AAV variants and each type of cancer.*

Results. *The mean age at diagnosis of AAV was 55.2 years and that at last visit was 59.5 years. The mean follow-up duration was 50.7 months. Four of 150 AAV patients had cancer (2.7%), and they got four different types of cancers including gastric cancer, lung cancer, prostate cancer and Non-Hodgkin lymphoma. Two patients exhibited gap-time from AAV to malignancy less than one year, and the rest of them exhibited gap-time of 8 and 6 years, respectively. The overall SIR of cancer in AAV patients was 1.43 (95% confidence interval 0.391, 3.671). The SIRs of cancer based on gender, and age at cancer or last visit, AAV variants and each type of cancer were not significant, either.*

Conclusion. *The risk of cancer is low in Korean patients with AAV.*

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic autoimmune vasculitides, which often involve small vessels of various organs from capillaries to arterioles (1). AAV consists of three variants according to clinical, laboratory and histological features including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (1-4). Because AAV can affect major organs such as heart, lungs, kidneys and nerves, intensive induction therapy based on high dose of glucocorticoid plus immunosuppressive drugs including cyclophosphamide and rituximab should be provided to patients with serious complications (5-8).

Not a few autoimmune diseases with chronic inflammation have been considered to lead to an increase in the incidence rate of cancer, such as rheumatoid arthritis (9), systemic lupus erythematosus (10), Sjögren's syndrome (11), systemic sclerosis (12) and inflammatory myopathy (13). Chronic inflammation of autoimmune diseases may be closely linked to cancer occurrence (14), and immunosuppressive drugs for treatment of them may induce impairment in immune surveillance to recognise cancer cells as well as directly play oncogenic roles (15). Therefore, we theoretically assume that AAV can also enhance the risk of cancer development with the same reasons.

The standardised incidence ratios (SIRs) of cancer in AAV patients were reported to range from 1.6 to 2.4 with significant 95% confidence interval (CI), compared to the general population and the most common cancers were urinary tract cancer, skin cancer, leukaemia and lymphoma (16-20). Meanwhile, the overall SIR of cancer in AAV is recently reduced due to changes in therapeutic regimens or decreases in exposure periods (21). Thus, the risk of cancer development in AAV patients is now controversial. In addition, most studies were conducted in North America and European

countries and furthermore, there is no report regarding the incidence rate and the type of cancer in AAV patients in Korea. Hence, in this study, we investigated the incidence rate and the type of cancer, and furthermore, estimated the SIRs of cancer according to totality, gender, age, AAV variants and each type of cancer in Korean patients with AAV.

Patients and methods

Patients

We retrospectively reviewed the medical records of 154 patients with AAV according to the inclusion criteria as follows: i) patients who had been classified as MPA, GPA and EGPA from October 2000 to April 2017 at Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital; ii) patients who fulfilled the American College of Rheumatology 1990 criteria for the classification of GPA and EGPA, and who were reclassified by the algorithm suggested by the European Medicines Agency in 2007 and then the Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides proposed in 2012 (1-4); iii) patients who were followed up for at least 12 weeks to determine relapse of AAV (22); iv) patients who had well-documented medical records to assess clinical manifestations and calculate vasculitis activity score represented by Birmingham vasculitis activity score (BVAS) and prognostic factors identified by five factor score (FFS (2009)) at diagnosis (23-25); v) patients who had the results of ANCA tests (1, 4). Cancers were searched by the 10th revised International Classification of Diseases (ICD-10) and the notice provided by Korean National Health Insurance Service. Among 154 AAV patients, four patients had got cancers at least more than two years before diagnosis of AAV: two patients had thyroid cancer, one patient had tongue cancer and one patient had gastric cancer. Therefore, we excluded these four patients and finally included 150 patients with AAV in this study. This study was approved by the institutional Review Board (IRB) of Severance Hospital (4-2017-0673), and the patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

Clinical and laboratory data and medications

We obtained ages at three different time-points, diagnosis of AAV, detection of cancer and last visit. We also collected gender and the follow-up duration as demographic data. The follow-up duration was defined as the period from diagnosis of AAV to the last visit in all patients. We counted the number of patients who had myeloperoxidase (MPO)-ANCA or perinuclear (P)-ANCA and proteinase 3 (PR3)-ANCA or cytoplasmic (C)-ANCA. We inquired into the initial clinical manifestations, BVAS including BVAS for GPA and FFS (2009). We also reviewed the use of glucocorticoid and immunosuppressive drugs, which had been administered until detection of cancer or last visit by the Korean Drug Utilization Review (DUR) system. P-ANCA and C-ANCA were detected by immunofluorescent assay. MPO-ANCA and PR3-ANCA were measured by ELISA kit for anti-PR3 and anti-MPO (Inova Diagnostics, San Diego, USA) before 2013, and by the novel anchor coated highly sensitive (hs) Phadia ELiA (Thermo Fisher Scientific/Phadia, Freiburg, Germany) using human native antigens, performed on a Phadia250 analyser after 2013. In four AAV patients with cancer, we also calculated the gap-time from diagnosis of AAV to detection of cancer and searched types of cancers.

Cancer and the standardised incidence ratios (SIRs)

We included only AAV patients with cancer, in whom cancers were confirmed on histology. We estimated the SIRs of cancer according to totality, gender, age, AAV variants and each type of cancer. Data of the crude incidence rate of cancer from the Korea Central Cancer Registry and data from the cancer statistics of 2013, which was published in December 2016, were used for calculating the SIRs (26). In addition, for computing the number of expected cases, the cancer incidence rate (cases per 100,000 person years) in the general population was multiplied by the corresponding number of patients in each category.

Statistical analyses

All statistical analyses were conducted using SPSS software (v. 23 for windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were done as number and the percentage. Significant differences in variables between patients with and without malignancy were compared using the Chi-square test and the Fisher's extract test for categorical data and the Mann-Whitney U test for continuous variables. To obtain 95% confidence interval (CI) for the SIRs, the Fisher exact test was used. *P*-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of 150 AAV patients were shown in Table I. The mean age at diagnosis of AAV was 55.2 years and that at last visit was 59.5 years. One hundred-three patients (68.7%) were female. The mean follow-up duration was 50.7 months. Eighty-one patients were classified as MPA, 38 patients as GPA and 31 patients as EGPA. Ninety-three patients (62.0%) had MPO-ANCA (or P-ANCA), 26 patients (17.3%) had PR3-ANCA (or C-ANCA) and 7 patients (4.7%) had both ANCAs. Thirty-eight patients (25.3%) had no ANCA. Among clinical manifestations at diagnosis of AAV, renal manifestation (59.3%) was the most frequently observed. The initial mean BVAS and FFS (2009) were 12.1 and 1.3. One hundred-twenty-nine patients (86.0) received glucocorticoid and 63 patients (42.0) received cyclophosphamide. Forty-four of 150 patients (29.3%) experienced relapse during the follow-up.

Comparison of variables between patients with and without cancer

Comparison analysis between patients with and without cancer was also shown in Table I. When we divided 150 AAV patients into the two groups according

Table I. Comparison of variables between AAV patients with and without cancer.

Variables	All patients (n=150)	Patients with cancer (n=4)	Patients without cancer (n=146)	*p*-value
Demographic data				
Age at diagnosis of AAV (years)	55.2 ± 15.3	56.3± 17.8	55.2 ± 15.3	0.894
Age at last visit (years)	59.5 ± 14.7	62.2± 12.8	59.4 ± 14.8	0.708
Female gender (n, (%))	103 (68.7)	1 (25.0)	102 (69.9)	0.056
Follow-up duration (months)	50.7 ± 49.6	71.3 ± 66.0	50.14 ± 49.3	0.403
Variants of AAV (n, (%))				0.553
MPA	81 (54.0)	3 (75.0)	78 (53.4)	
GPA	38 (25.3)	1 (25.0)	37 (25.3)	
EGPA	31 (20.7)	0 (0)	31 (21.2)	
ANCA at diagnosis of AAV (n, (%))				
MPO-ANCA (or P-ANCA)	93 (62.0)	2 (50.0)	91 (62.3)	0.616
PR3-ANCA (or C-ANCA)	26 (17.3)	0 (0)	26 (17.8)	0.353
Both ANCAs	7 (4.7)	0 (0)	7 (4.8)	0.654
ANCA negative	38 (25.3)	2 (50.0)	36 (24.7)	0.250
Clinical manifestations at diagnosis of AAV (n, (%))				
General manifestation	67 (44.7)	2 (50.0)	65 (44.5)	0.828
Cutaneous manifestation	34 (22.7)	1 (25.0)	33 (22.6)	0.910
Mucous membranes/Eyes manifestation	12 (8.0)	0 (0)	12 (8.2)	0.550
Ear Nose Throat manifestation	52 (34.7)	2 (50.0)	50 (34.2)	0.514
Chest manifestation	80 (53.3)	3 (75.0)	77 (52.7)	0.379
Cardiovascular manifestation	44 (29.3)	2 (50.0)	42 (28.8)	0.357
Gastrointestinal manifestation	10 (6.7)	0 (0)	10 (6.8)	0.588
Renal manifestation	89 (59.3)	2 (50.0)	87 (59.6)	0.700
Nervous systemic manifestation	48 (32.0)	0 (0)	48 (32.9)	0.164
BVAS or BVAS for GPA at diagnosis of AAV	12.1 ± 7.7	10.8 ± 4.7	12.2 ± 7.7	0.714
FFS (2009) at diagnosis of AAV	1.3 ± 1.0	1.5 ± 1.0	1.3 ± 1.0	0.626
Medications administered during the follow-up or prior to cancer (n, (%))				
Glucocorticoid	129 (86.0)	4 (100.0)	126 (86.3)	0.427
Cyclophosphamide	63 (42.0)	2 (50.0)	61 (41.8)	0.742
Mycophenolate mofetil	10 (6.7)	0 (0)	10 (6.8)	0.588
Azathioprine	41 (27.3)	0 (0)	41 (28.1)	0.214
Calcineurin inhibitor	9 (6.0)	0 (0)	9 (6.2)	0.609
Rituximab	15 (10.0)	0 (0)	15 (10.3)	0.499
Methotrexate	13 (8.7)	0 (0)	13 (8.9)	0.532
Relapse during the follow-up (n, (%))	44 (29.3)	0 (0)	44 (30.1)	0.192
Gap-time from AAV to cancer (months)		3.8 ± 3.8		

Values are expressed as mean and standard deviation or n (%).
AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five factor score.

to the presence of cancer and compared all variables between them. First of all, four patients turned out to get cancers after diagnosis of AAV and this meant the incidence rate of cancer of 2.7% in Korean patients with AAV. In terms of demographic data, variants of AAV, ANCA positivity and the initial clinical manifestations, BVAS and FFS (2009), we could find no meaningful differences between patients with and without cancer. Medications administered during the follow-up or prior to cancer and relapse rate did not differ between the two groups. The mean gap-time form AAV to cancer was 3.8 years.

Characteristics of patients with cancer

Characteristics of patients with cancer were described in Table II. Among four patients with cancer, three patients were classified as MPA and one patient was as GPA. Three patients were male. Age at diagnosis of AAV ranged from 32 to 73 years and the follow-up duration was up to 144 months. Two MPA patients had MPO-ANCA (or P-ANCA), but others had no ANCAs. Ages at detection of cancer ranged from 40 to 74 years. Two patients exhibited gap-time from AAV to malignancy less than one year, and the rest of them exhibited gap-time of 8 and 6 years, respectively. Four patients got four different types of cancers including gastric cancer, lung cancer, prostate cancer and Non-Hodgkin lymphoma. Until detection of cancer, glucocorticoid was administered to all patients with cancer, while cyclophosphamide was administered to only two patients with cancer, who had more serious comorbidities such as chronic kidney disease ≥ stage 3. One patient with cancer died of diffuse alveolar haemorrhage associated with AAV or pneumonia rather than non-Hodgkin lymphoma.

Standardised incidence ratio of cancer

The overall SIR of cancer in 150 Korean patients with AAV was estimated as 1.43 compared to the general generation, but it was not statistical significant (Table III). We performed subgroup analysis of the SIRs of cancer based on gender, and age at cancer or last visit and AAV variants, but we found no significant SIRs of cancer (Table III). Furthermore, we also calculated SIRs based on each type of cancer, but found no meaningful SIRs of cancer either (Table III).

Discussion

In this study, we investigated the incidence rate and the type of cancer, and estimated the SIRs of cancer according to totality, gender, age, AAV variants and each type of cancer in Korean patients with AAV. First, the incidence rate of cancer in Korean patients with AAV was 2.7% (4 of 150 patients) during the follow-up. Second, four individuals had four different types of cancers including gastric cancer, lung cancer, prostate cancer and Non-Hodgkin lymphoma and the mean gap-time form AAV to cancer was 3.8 years. Third, both the overall SIR of cancer at all sites and SIRs of cancer based on gender, age at cancer or last visit, AAV variants and each type of cancer were not associated with an increase in cancer development in Korean patients with AAV. We conclude that AAV and its therapeutic regimens might not increase the risk of cancer development in Korean patients with AAV compared to the general population, unlike previous reports conducted in North

Table II. Characteristics of AAV patients with cancer.

Patient's number	Variants	Gender /Age at diagnosis of AAV (years)	The follow-up duration (months)	ANCA	Age at detection of cancer (years)	The gap-time from AAV to cancer (months)	Type of cancer	Immunosuppressive drugs prior to cancer	Comorbidities other than cancer	Death	Cause of death
1	MPA	F/32	144	ANCA negative	40	96	Gastric cancer	Glucocorticoid	None	No	N/A
2	MPA	M/65	21	MPO-ANCA (or P-ANCA)	66	6	Lung cancer	Glucocorticoid	ILD	No	N/A
3	MPA	M/73	10	MPO-ANCA (or P-ANCA)	74	6	Prostate cancer	Glucocorticoid Cyclophosphamide	ESRD, DM	No	N/A
4	GPA	M/55	110	ANCA negative	61	72	Non-Hodgkin Lymphoma	Glucocorticoid Cyclophosphamide	CKD, DM, HTN, ILD	Yes	DAH

Values are expressed as mean and standard deviation or N (%).
AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; ILD: interstitial lung disease; ESRD: end stage renal disease; DM: diabetes mellitus; CKD: chronic kidney disease; HTN: hypertension; N/A: not applicable; DAH: diffuse alveolar haemorrhage.

Table III. Standardised incidence ratios of cancer (patient-years).

Variables	Expected cases	Observed cases	SIRs (95% CI)
Total (n=150)	2.79	4	1.43 (0.391, 3.671)
Gender			
Male (n=47)	0.84	3	3.57 (0.737, 10.437)
Female (n=103)	1.93	1	0.52 (0.013, 2.887)
Age at cancer or last visit			
< 64 years (n=82)	1.52	2	1.32 (0.159, 4.753)
≥ 65 years (n=68)	1.27	2	1.58 (0.191, 5.689)
AAV variants			
MPA (n=81)	1.28	3	2.34 (0.483, 6.849)
GPA (n=38)	0.79	1	1.27 (0.032, 7.053)
Malignancies			
Gastric cancer	2.77	1	0.36 (0.009, 2.012)
Lung cancer	0.73	1	1.37 (0.035, 7.633)
Prostate cancer*	0.41	1	2.44 (0.062, 13.590)
Non-Hodgkin lymphoma	0.36	1	2.78 (0.070, 15.477)

*Prostate cancer occurs only in male patients. Therefore the number of patients included was forty-seven male patients.
SIRs: standardised incidence ratios; CI: confidence interval; AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis.

American and European countries (18-20).

There was discordance in type of cancer in AAV patients between previous studies and ours. AAV patients in previous studies exhibited cancers bladder cancer, non-melanoma skin cancer, leukaemia and lymphoma with significant SIRs (16-20). Meanwhile, our patients exhibited four different types of cancers including gastric cancer, lung cancer, prostate cancer and non-Hodgkin lymphoma without significant SIRs. According to cancer statics of Korean general population in 2013, all four cancers observed in our patients were included within the most common ten cancers (26). Thus, if patients strongly ask for cancer-screening, physicians may recommend screening tests for cancers with the higher incidence rates in each ethnicity and countries.

Immunosuppressive drugs can provoke cancer through impairment in cancer cell surveillance or direct mutagenesis (15). Among various drugs, cyclophosphamide has been considered closely linked to urinary tract cancer, particularly bladder cancer. Bladder cancer can occur 10 years or greater after the first exposure of cyclophosphamide and the approximate SIR of cancer range from 3.6 to 7.2 (15). Furthermore, the cumulative dose of cyclophosphamide is another risk of bladder cancer (27). In previous study the cumulative dose of cyclophosphamide of 50g or greater increased the risk of bladder cancer as high as 64% (15, 16). In this study, two of four patients with cancer received cyclophosphamide. However, they exhibited no bladder cancer, but prostate cancer and non-Hodgkin lymphoma. Patient 3 had received intravenous cyclophosphamide bimonthly 3 times due to recurrent infection. The cumulative dose was 3,000 mg and prostate cancer was diagnosed 2 months after the last exposure of cyclophosphamide (Table II). Patient 4 had taken oral cyclophosphamide for 6 years. The cumulative dose was 120,900 mg and non-Hodgkin lymphoma developed while taking oral cyclophosphamide (Table II). There was no pattern of cancer development proportional to its cumulative dose. Thus, we conclude that cyclophosphamide may be associated with impairment in malignant cell surveillance rather than direct mutagenesis in AAV patients in Korea, unlike North American and European countries.

A previous study reported the higher SIR of cancer in GPA patients than MPA patients (1.9 vs. 1.2), and attributed the difference to two reasons: first, GPA patients exhibit relapse more frequently than MPA patients, which

needs the more cumulative dose and the longer use of immunosuppressive drugs, and second, MPA patients showed the higher mortality rate than GPA patients (20). In this study, three of 81 MPA patients had cancers and one of 38 GPA patients got cancer, and the SIRs of cancer in MPA (2.34) and GPA patients (1.27) did not differ. Furthermore, all four patients with cancer experienced no relapse. Thus, we assume that AAV variants may not contribute to cancer development in AAV patients in Korea.

This study has two advantages. First, this is the first report regarding cancer development in Korean patients with AAV, which may provide a valuable reference on cancer development in AAV patients in North Eastern Asia. Second, all patients were classified as AAV and followed up in a single centre, which may minimise the intercentric bias. However, our study has several limitations. First, because this study was retrospectively conducted, data were mostly depended on the medical records, and thus there might be missing data. Second, because the number of patients who had cancers was only four, the statistical power of our study was not high enough to represent all Korean patients with AAV. Third, although the prevalence of melanoma or non-melanoma skin cancer does not rank within 10 most common cancers in Korea, unlike North America or European countries, we are not sure that we had not missed patients with non-melanoma skin cancers in this study. We hope that future studies with the larger number of patients in our prospective cohort will clarify the risk of cancer in AAV patients in Korea. In conclusion, AAV and its therapeutic regimens may not increase the risk of cancer development in Korean patients with AAV, compared to the general population, unlike previous reports conducted in North American and European countries.

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