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Original article

Incidence of malignancy in primary Sjögren's syndrome in a Chinese cohort

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Abstract

Objectives. To evaluate the incidence of malignancies in a cohort of Chinese patients with primary Sjögren's syndrome (pSS) and to identify the risk factors of malignancy in pSS patients.

Methods. A retrospective analysis was carried out in 1320 pSS patients who were recruited in Peking Union Medical College Hospital from 1990 to 2005 and were followed up for an average of 4.4 years. Among them, 29 patients developed malignancies. Standardized incidence ratios (SIRs) were calculated along with 95% CIs. Clinical characteristics were compared between patients with and without malignancies, as well as patients with haematological and non-haematological tumours.

Results. Of the pSS patients, 2.2% developed malignancies during follow-up. Total SIR and SIR for lymphoma were 3.25 and 48.1, respectively. Different types of malignancy were observed including eight lymphomas, two myeloid myelomas and 19 solid tumours, which consisted of invasive thymoma, breast cancer, lung cancer, gastrointestinal adenocarcinoma, hepatoma, squamous cell carcinoma of tongue, uterine cervix cancer, renal carcinoma, thyroid carcinoma and mucoepidermoid carcinoma of parotid gland. Risk factor analysis showed that lymphadenopathy, enlargement of parotid glands, monoclonal immunoglobulin and absence of hypergammaglobulinaemia were correlated with malignancies.

Conclusions. The current study confirms the increased incidence of lymphoma in Chinese patients with pSS, with the majority of B-cell non-Hodgkin's lymphoma. Associations between pSS and other malignant tumours such as myeloid myeloma, mouth cancer, breast cancer and thymoma need to be further observed.

Key words: Sjögren's syndrome, Malignancy, Lymphoma.

Introduction

Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease characterized by exocrine involvement, also known as autoimmune epithelitis [1]. Although it has been shown that patients with pSS have a lifespan not significantly different from that of the normal population, pSS patients have a greater risk of developing lymphoproliferative malignancy [2, 3]. Lymphoma is also one of the causes of death in pSS patients. Several studies have confirmed a high risk of lymphoma for pSS with risk factors of 8.7–44.4 [4–10] and a lifetime risk of ~5–10% [11, 12]. A meta-analysis published in 2005 searched 20 studies for relative risk (RR) of non-Hodgkin's lymphoma (NHL) in RA, pSS and SLE and found extreme heterogeneity among the studies, but a consistently high risk of NHL development in pSS patients [13]. Several predictors of lymphoma development have been identified, including clinical signs such as lymphadenopathy, swollen salivary glands, palpable purpura or skin vasculitis, peripheral nerve involvement, leg ulcers, use of cytotoxic drugs and laboratory predictors such as anaemia, lymphopenia and low levels of complement [2, 4, 9, 14]. Other cancers also occur in patients with pSS [9].

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However, according to some studies, SS did not appear to be associated with a greater prevalence of cancer, other than lymphoma, than the general population. Until now, there have been no data on the incidence of malignancy in patients with pSS reported from China. In this study, we assessed standardized incidence ratios (SIRs) of malignancies in a cohort of Chinese pSS patients, as well as clinical and laboratory risk factors of pSS patients with malignancies.

Patients and methods

Patients

All patients admitted to Peking Union Medical College Hospital between 1990 and 2005, with a diagnosis of pSS, as confirmed by revised version of classification criteria for SS proposed by the American–European Consensus Group [15], were eligible for this study. The study has been approved by ethical committees from Peking Union Medical College Hospital, and informed consent was signed according to the Declaration of Helsinki. Malignant tumours were diagnosed according to pathological results, fulfilling International Classification of Diseases (ICD-10) criteria. The type of lymphoproliferative malignancy was reclassified by the 2001 World Health Organization (WHO) classification for tumours of haematopoietic tissues. Medical charts of these patients were systematically reviewed for demographic data, clinical features, laboratory findings, as well as treatments. Hypergammaglobulinaemia was defined as an increased level of any immunoglobulin subtype, including IgG (normal range: 700–1700 mg/dl), IgA (normal range: 70–380 mg/dl) and IgM (normal range: 60–250 mg/dl). ANA was tested with IIF assay, by which a titre of $>$1:160 was defined as positive. Patients were followed up for different periods of time and any recorded malignant tumour was documented.

Variables in the risk factor analysis

As possible risk factor variables for malignancy development we included clinical variables, such as dry mouth, dry eyes, lymphadenopathy, swollen salivary glands, palpable purpura, skin vasculitis, peripheral nerve involvement, and laboratory predictors such as ANA, anti-Ro, anti-La, hypergammaglobulinaemia, monoclonal immunoglobulinaemia, as well as low levels of complement.

Statistical analysis

Calculation of SIRs. Expected risks for malignancies were calculated by comparison with the background population (region of China) matched for age, sex and calendar period [16, 17]. The SIR was calculated by dividing the observed by the expected risk, 95% CIs were calculated as well. RR was calculated by univariant analysis.

Correlation analysis. Data were analysed using SPSS10.0. To analyse the correlation between clinical variables and incidence of malignancy, chi-square test was used with $P < 0.05$ denoting significant statistical difference.

Results

Demographic characteristics of pSS accompanied by malignancy

A total of 1320 pSS patients of Han ethnicity were available for analysis. The majority was female (1201, 91%). Mean (S.D.) age was 39.0 (4.2) years. Patients were followed up for an average of 4.2 (1.6) years. Malignancy occurred in 29 (2.2%) patients (27 females and 2 males), including 8 (0.61%) NHLs. Of all cases with malignancy, age at diagnosis of tumour was 50.7 (12.0) years, age at diagnosis of pSS was 44.7 (13.2) years and duration from diagnosis of pSS to development of tumour was 5.8 (4.3) years. All patients with haematological malignancies were diagnosed after the diagnosis of pSS. Out of 19 patients with solid tumours, 14 were diagnosed after pSS, 3 were diagnosed coincidentally at the diagnosis of pSS and 2 were diagnosed before pSS.

SIRs for lymphomas and other tumours

Table 1 gives the observed and expected number of malignancies with the corresponding SIRs and 95% CIs. In this group, 29 tumours were detected during 5544 years of observation. There was a significantly increased SIR in total malignancies (3.25; 95% CI 2.12, 4.52) as well as in lymphoma (48.1; 95% CI 20.73, 94.76) and multiple myeloma (MM) (37.9; 95% CI 4.58, 136.7). For non-haematological tumours, the observed increase was small and not statistically significant (SIR 2.12; 95% CI 1.27, 3.31). Table 2 lists SIRs of lymphoma in pSS patients from different studies in the USA, Finland, Italy, Britain and Sweden, which shows the highest in China.

Table 1 SIRs of malignancies in Chinese pSS patients

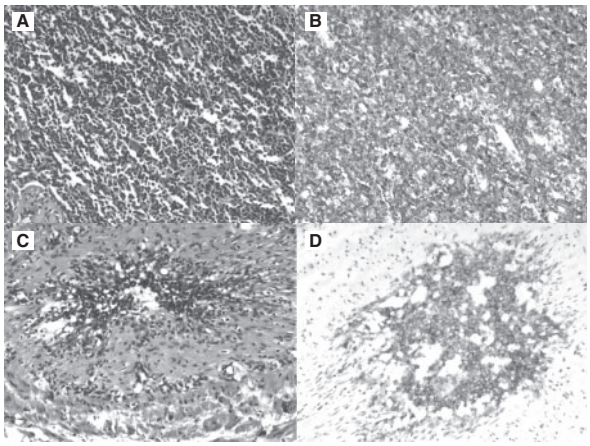
	Observed, *n*	Expected, *n*	SIR	95% CI
Total malignancy	29	8.9	3.25	2.12, 4.52
Lymphoma	8	0.17	48.1	20.73, 94.76
Multiple myeloma	2	0.05	37.9	4.58, 136.7
Non-haematological tumour	19	8.68	2.12	1.27, 3.31

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Table 2 Comparison of SIR for lymphomas in different studies

	Year	Country	SIR (95% CI)	Lymphoma, *n*	No. of patients	Follow-up time, patient-year
Kassan *et al*. [4]	1978	USA	44.4 (16.7, 118.4)	4	142	22 (1099)
Kauppi *et al*. [5]	1997	Finland	8.7 (4.3, 15.5)	11	676	22 (5336)
Valesini *et al.* [6]	1997	Italy	33.3 (17.3, 64.0)	9	295	25
Davidson *et al*. [7]	1999	Britain	14.4 (4.7, 44.7)	3	100	8
Pertovaara *et al*. [8]	2001	Finland	13 (2.7, 38)	3	110	15
Lazarus *et al*. [9]	2006	Britain	37.5 (20.7, 67.6)	11	112	10.8 (1210)
Theander *et al*. [10]	2006	Sweden	15.57 (7.8, 27.9)	11	507	7 (2464)
This study	2009	China	48.1 (20.7, 94.8)	8	1320	4.2 (5544)

Fig. 1 Representative histopathological pictures from pSS patients. (**A**) MALT lymphoma of salivary glands. The characteristic lymphoepithelial lesions are extensively infiltrated and surrounded by pale cells (HE ×150). (**B**) Immunostaining shows CD20-expressing B cells. (**C**) Intravascular large B-cell lymphoma in a subcutaneous blood vessel (HE ×150). (**D**) Immunostaining with CD20 shows diffuse sheets of B cells.



Types of malignancy in pSS

Ten out of 29 (34.5%) pSS patients developed haematological tumours, including 8 NHL patients and 2 MM patients. Another 19 (65.5%) patients were diagnosed with solid tumours. Among eight (27.6%) NHL patients, seven (24.1%) were B-cell NHL patients and only one was a T-cell NHL patient. The pathological pattern of B-cell NHL included two diffused large B lymphomas (DLBLs), two lymphomas of mucosa-associated lymphoid tissue (MALT), one intravascular large B-cell lymphoma and two B-cell lymphomas unclassifiable. Four B-cell NHLs were confirmed by parotid biopsy. Figure 1 shows representative histopathological pictures of MALT and intravascular large B-cell lymphoma.

Figure 2 illustrates types of solid tumours, including breast caner in four (13.8%); invasive thymoma, adenocarcinoma of stomach, adenocarcinoma of colon, squamous cell carcinoma of tongue and lung cancer in two of each (6.9%); liver cancer, cervical carcinoma, renal cancer, thyroid gland tumour and mucoepidermoid carcinoma of parotid gland in one of each (3.4%).

Clinical characteristics of pSS patients with malignancies

Clinical characteristics in patients with and without malignancies were compared as shown in Table 3; lymphadenopathy, swollen salivary glands and monoclonal immunoglobulin were more frequent in patients with malignancies ($P < 0.05$), whereas the percentage of hypergammaglobulinaemia was low in patients with malignancies ($P < 0.05$). The highest level of IgG was 8250 mg/dl in a patient without malignancy and 6220 mg/dl in a patient with malignancy. Monoclonal immunoglobulin was found in 12 (41.4%) patients with malignancies, of which 10 were IgG type; IgA and IgM type in one of each. In terms of papable purpura, lung involvement, liver involvement, peripheral nerve involvement or other clinical parameters, there were no statistical differences between patients with and without malignancies ($P > 0.05$).

Comparisons between patients with haematological malignancies and those with solid tumours are shown in Table 4. Persistent splenomegaly was observed in two patients with lymphoma, whereas no patient with non-haematological tumour had splenomegaly ($P < 0.05$). Enlargement of parotid glands occurred more frequently in patients with haematological malignancies, whereas the anti-SSB-positive rate was lower in patients with haematological malignancy ($P < 0.05$). Although the percentage of monoclonal immunoglobulin was higher in patients with malignancy than in those without malignancy, there was no statistical significance.

RRs of different predictive factors for malignancy in pSS patients

As listed above, lymphadenopathy, swollen salivary glands, monoclonal immunoglobulin and absence of hypergammaglobulinaemia were four predictive risk factors for development of malignancy in pSS patients. We further analysed the RR for malignancy in patients who had any of one, two, three and three plus four risk factors.

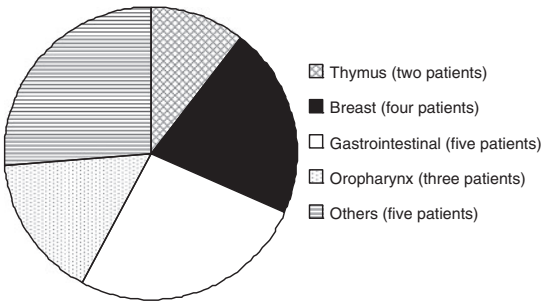
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Table 5 illustrates the results: the more risk factors the patients possessed, the higher RR they had.

Discussion

According to literature, in pSS patients, the overall incidence of all cancers is 1.42–2.6 times that in the general population, but the increased RR of malignancy was almost entirely due to the excess occurrence of lymphoma, of which the SIR of lymphoma varied from 8.7 to 44.4 [2, 4–10]. In this study, the overall incidence of malignant tumours was 2.2%; 0.67% of the pSS patients developed lymphoma. Since the incidence of lymphoma in China was 3.15/100 000, the calculated SIR of lymphoma in pSS was 48.1, the highest among the literature.

Fig. 2 Types of solid tumour in pSS patients. Others include lung cancer (two patients), cervical carcinoma (one patient), renal cancer (one patient) and thyroid cancer (one patient).



Regarding the type of malignancy in these Chinese pSS group, eight (27.6%) patients suffered from lymphoma, mostly B-cell NHL, which accounted for 87.5% of all lymphomas, including DLBL, MALT and intravascular B-cell lymphoma. The result is consistent with previous studies from other countries, in which the major type of lymphoma with pSS is B-cell lymphoma, DLBL and lymphoma with MALT predominated. Interestingly, in this study, 50% of the NHL patients were confirmed by parotid gland biopsy, suggesting chronic exocrine gland inflammation as grounds for the development of lymphoid malignancies [2, 4, 6, 8–10]. Furthermore, except for pSS, an increased risk of DLBL was also observed in patients with RA and autoimmune haemolytic anaemia [18]. The mechanisms underlying the development of B-cell lymphomas in SS potentially include defects in apoptosis, persistent antigenic stimulation, mutagenicity of B cells and T-cell modulation, such as B-cell activating factor of the TNF family (BAFF) or type 1 interferon [12, 19, 20]. Studies also bring to light a new and interesting finding that low peripheral $CD4^+$ count or low $CD4^+/CD8^+$ ratio may be an important risk factor for lymphoma in patients with SS [10, 21]. In addition, it was found that >14% of the SS patients had oligoclonal or monoclonal B-cell proliferation, 20–30% of the SS patients develop ectopic germinal centre (EGC) in exocrine glands, and it is speculated that monoclonal proliferated B cells existed mainly in EGC, and the formation of EGC might be a predictor of malignancy [22]. Notably, in our study, 41.4% of the pSS patients with malignancies and 70% of the pSS patients with haematological malignancies were detected to have monoclonal

Table 3 Characteristics of pSS patients with and without malignancies

	pSS with malignancies ($n = 29$), %	pSS without malignancies ($n = 1291$), %
Female	93.1	90.0
Dry mouth (symptom)	96.5	84.9
Dry eyes (symptom)	93.1	77.0
Lymphadenopathy*	20.7	7.7
Enlargement of salivary glands*	44.8	28.0
Papable purpura	13.8	13.4
Lung involvement	13.8	25.3
Liver involvement	24.1	20.0
Persistent splenomegaly	6.9	4.5
Peripheral nerve involvement	0	11.7
Neutropenia	34.5	31.9
Monoclonal immunoglobulin*	41.4	18.6
Hypergammaglobulinaemia*	31.0	60.0
ANA	82.8	83.0
Anti-Ro/SSA	72.4	83.0
Anti-La/SSB	37.9	40.7
Hypocomplementaemia	6.9	14.4
Focal infiltration of lymphocytes in labial salivary glands	89.7	90.6

Values are shown as percentages unless otherwise indicated. Lung involvement including interstitial lung disease, nodular and bullae. *$P < 0.05$.

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Table 4 Comparison of clinical manifestations between patients with haematological malignancies and those with solid tumours

	Patients with haematological malignancies ($n = 10$)	Patients with solid tumours ($n = 19$)
Gender (female : male)	9:1	18:1
Age at diagnosis of malignancy, mean (S.D.), years	48.8 (15.0)	51.5 (7.8)
Dry mouth	100	94.7
Dry eyes	100	89.5
Lymphadenopathy	20	21.1
Enlargement of salivary glands*	70	31.6
Persistent splenomegaly*	20	0
Papable purpura	10	15.8
Monoclonal immunoglobulin	60	31.6
Leg ulcers or skin vasculitis	20	10.5
Neutropenia	40	31.6
Hypergammaglobulinaemia	30	31.6
Hypocomplementaemia	10	5.3
ANA	70	89.5
Anti-Ro/SSA	60	78.9
Anti-La/SSB*	10	52.6

Values are shown as percentages. *$P < 0.05$.

Table 5 RRs of different predictive factors for malignancy in pSS patients

No. of risk factors	With malignancy, *n* (%)	Without malignancy, *n* (%)	RR (95% CI)	*P*-value
0	2 (6.9)	458 (35.5)		
1	8 (27.6)	545 (42.2)	3.361 (0.710, 15.908)	0.122
2	14 (48.3)	249 (19.3)	12.378 (2.791, 54.892)	<0.001
3	4 (13.8)	39 (3.02)	23.487 (4.170, 132.295)	0.001
≥3[a]	5 (17.2)	39 (3.02)	29.359 (5.515, 156.287)	<0.001

RR values were compared with patients with none of the risk factors. [a]No patient without malignancy had four risk factors; only one patient with malignancy had all four risk factors, therefore, three or more were applied.

immunoglobulin in serum that is much higher than non-tumour SS patients, suggesting that the monoclonal proliferation of B cells might transform into malignancy.

Two pSS patients were diagnosed as MM in the current study with an SIR of 37.9. There are some reported cases of MM associated with pSS, although no definite correlation was found between pSS and MM [23, 24]. The exact mechanism remains under speculation; however, similar immunological disorders may play a role in transforming benign monoclonal gammaglobulin-producing plasma cells into malignant plasma cells.

Evidence is accumulating that chronic inflammatory response and especially localized chronic inflammation is responsible for an increased risk of malignancy [25]. In this study, we found cases of pSS with squamous cell carcinoma of tongue and mucoepidermoid carcinoma of the parotid gland, which might be related to local chronic inflammation or chronic damage from loss of saliva fluid.

Interestingly, in this study, there were four pSS patients diagnosed with thymoma, including two invasive thymomas that were reported as malignancies in our results. Thymomas are highly associated with autoimmune diseases [26]; however, thymoma as a complication of SS is rare, only a few case have reported association of thymomas with pSS [27].

Previously proposed risk factors of malignancy in pSS such as parotid gland enlargement, purpura rash or skin vasculitis, peripheral neuropathy and hypocomplementaemia were analysed in this study, which showed that the percentages of lymphadenopathy, swollen salivary glands and monoclonal immunoglobulin were consistently higher in patients with malignancies. Moreover, in comparison with those of non-haematological tumours, enlargement of parotid gland and persistent splenomegaly occurred more frequently in patients with haematological tumours, indicating that enlargement of parotid gland and persistent splenomegaly were risk factors for

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haematological tumours in pSS patients. However, in patients with malignancies, the percentage of hypergammaglobulinaemia was statistically lower. Surprisingly, in this study, patients with haematological malignancies were found to have a lower concentration of anti-SSB (anti-La) antibodies than those with solid tumours. As anti-La antibody triggers the apoptotic process and mediates inhibition of apoptotic cell uptake [28, 29], the result suggested that anti-La antibody might act on haematological cells more than somatic cells, therefore, the non-existence of anti-La antibody might be a protective factor for haematological malignancies. Further observation is needed.

In summary, based on these data it was found that pSS patients have a high incidence of malignancy, of which haematological malignancies, including NHL and MM, are associated with pSS more than solid tumours. Among the clinical and serological parameters that have been associated with lymphoma development in patients with pSS, the presence of parotid gland enlargement and monoclonal immunoglobulin constitute the main risk factors. There is evidence that some kinds of solid tumour such as oral cancer and thymoma might be associated with pSS, but that would need to be further studied.

Rheumatology key messages

- This is the first study to report occurrence of malignancies in pSS patients from China.
- SIRs of lymphoma in this Chinese cohort is 48.1, which is the highest among the literature.
- Risk factors of developing malignancies in Chinese pSS patients include enlargement of parotid glands and monoclonal immunoglobulin.

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