Sjögren Syndrome and Cancer

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KEYWORDS

• Sjögren syndrome • Malignancy • Lymphoma • Salivary glands • Amyloidosis
• Autoimmune disease • Lymphoproliferative disorders

KEY POINTS

- Patients with primary Sjögren syndrome (pSS) have a 10-fold to 44-fold greater risk of lymphoma than healthy individuals.
- Among lymphomas noted in pSS patients, 90% are due to mucosa-associated lymphoid tissue lymphoma, diffuse large B-cell lymphoma, or marginal zone lymphoma.
- Breast cancer can be overstaged due to misinterpretation of axillary metastasis.
- Head and neck cancers can present as rapidly developing neck lymphadenopathy.
- Lung cancer is found in excess among those with pulmonary disease.

Henrik Sjögren in 1933 presented clinical and histologic findings of 19 women who had symptomatic sicca.[1] The eponymous disease Sjögren syndrome (SS) ranges from only exocrine gland involvement with sicca to systemic, multiorgan autoimmune disease. SS is classified as either primary SS (pSS) or secondary SS, the latter accompanied by another connective tissue disease, such as systemic lupus erythematosus (SLE), with rheumatoid arthritis (RA) found most commonly.[2]

GENERAL CONSIDERATIONS

Among the systemic manifestations, benign or malignant lymphoproliferation may be a prominent part of this syndrome.[3] Several studies show a high incidence of

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malignancy in SS, the most common being lymphoma.[4–6] When studied, no increased all-cause mortality was detected for patients with pSS compared with the general population (Supplemental Table 1). When pSS subgroups were compared, however, higher mortality due to lymphoproliferative malignancy was found in patients fulfilling the American-European Consensus Criteria for Sjögren's Syndrome, with the strongest predictor for an unfavorable outcome being low C3 and/or C4 levels at the time of diagnosis.[7] A study published in 2010 investigated tumors in pSS and noted that with a prevalence of 5%, lymphoma was the most common tumor.[8] This was confirmed further by Nishishinya and colleagues.[9] pSS patients have a 10-fold to 44-fold greater risk of lymphoma than healthy individuals. This risk is higher than that reported for SLE or RA.[10] Diagnosis of lymphoma prior to a diagnosis of an underlying or undiagnosed SS is not unusual; in a significant proportion of patients, particularly in men, pSS remains undiagnosed until after lymphoma diagnosis.[11] A summary of all studies of lymphoma in SS is given in **Table 1**.

MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA

Lymphoma is thought to occur due to the chronic stimulation of B cells by autoantigens in a cascade that is initiated by stimulation at the level of the target tissue by autoimmune damage of polyclonal B cells, especially B cells that secrete rheumatoid factor.[12] The risk of a malignant B-cell transformation is mediated by the likelihood that prooncogenic elements contribute to an aberrant increase in B-cell survival.[10,13] The World Health Organization (WHO) classification categorizes lymphomas into B-cell or T-cell/natural killer–cell neoplasms, which in turn are further designated into various subtypes.[14] T cells predominate in the infiltration of the salivary glands of patients with pSS.[15] Despite this, lymphomas that occur in pSS patients predominantly are of B-cell origin, with only a mere 2% of lymphomas attributable to T-cell lineage.[10]

Among lymphomas noted in pSS patients, 90% are due to mucosa-associated lymphoid tissue (MALT) lymphoma, diffuse large B-cell lymphoma, or marginal zone lymphoma.[16–21] Evidence shows that pSS patients have a 22-fold to 260-fold higher risk of developing parotid gland B-cell lymphoma and a 90-fold to 1000-fold higher risk of developing parotid gland MALT lymphoma in comparison with the general population.[10,22–24] Lymphoma, however, can target a range of tissues; the primary sites of lymphoma development in pSS patients in descending order include salivary; lungs; gastric; ocular; oral; spleen; liver; thymus/intestines; skin; and lastly bone.[10,25–32]

There are a variety of risk factors. Patients with young onset of the pSS develop lymphoma more frequently than those with a much later onset.[33,34] The glandular, cutaneous, and lymphadenopathy domains of EULAR Sjögren's syndrome disease activity index were noted to be the most prominent predictors.[10,35] A majority of pSS lymphomas arise in the parotid glands, and a history of parotid enlargement is a risk factor.[10] Enlarged lymph nodes along with a history of spleen enlargement have been reported as another risk marker for lymphoma.[10,16,17,36–39] In addition, low-grade fever, purpura, and skin ulcers have been associated with lymphoma.[10] There also is a notable association between monoclonal cryoglobulinemic vasculitis and lymphoma.[18,32,38–42]

$CD4^+$ T cell lymphocytopenia has been reported as a significant predictor of lymphoproliferative disease, which is noted mainly in association with anti-Ro (or Sjogren's syndrome A) antibodies,[41] although having a positive antinuclear antibody test has not been implicated in lymphoma risk.[10,38,43,44] Controversy exists regarding the prognostic role of anti-Ro and anti-La (or Sjogren's syndrome B) antibodies. pSS negative for anti-Ro and anti-La antibodies is characterized by a lower risk of lymphoma, by a lower level of B-cell clonal expansion, and by a lower prevalence of

Table 1
Studies of lymphoma in Sjögren syndrome with calculated standardized incidence ratios and 95% CIs

Reference, Year	Location	Number Lymphoma/ Cohort		Standardized Incidence Ratio (95% CI)	Follow-up Length/Patient-Years
Kassan et al,[124] 1978	USA	4	142	44.4 (16.7, 118.4)	8.1[a]/109
Kauppi et al,[125] 1997	Finland	22	676	8.7 (4.3, 15.5)	NG/5336
Valesini et al,[37] 1997	Italy	9	295	33.3 (17.3, 64.0)	5.9[a]/1756
Davidson et al,[29] 1999	UK	3	100	14.4 (4.7, 44.7)	8 (duration)
Pertovaara et al,[30] 2001	Finland	3	110	13 (2.7, 38)	15 (duration)/1015
Zintzaras et al,[20] 2005	Multiple	30	1300	18.8 (9.5–37.3)	22[b]
Lazarus et al,[5] 2006	UK	11	112	37.5 (20.7, 67.6)	10.8[a]/1210
Theander et al,[41] 2006	Sweden	11	286	15.57 (7.77, 27.85)	8[b]/2464
Brito-Zerón et al,[44] 2007	Spain	9	266	NG	8.66[a]
Zhang et al,[4] 2010	China	8	1320	48.1 (20.7, 94.76)	4.2[a]/5544
Baimpa et al,[16] 2009	Greece	40	536	NG	2.6[b]
Weng et al,[126] 2012	Taiwan	23 3	6911 941	F: 7.08 (4.25, 10.3) M: 3.10 (0.64, 9.05)	3.5[a]/27,246
Solans-Laqué et al,[32] 2011	Spain	11	244	15.6 (8.7–28.2)	8.6[b]/NG
Johnsen et al,[27] 2013	Norway	7	443	9 (7.1, 26.3)	8[b]/3813
Liang et al,[6] 2014	Multiple	104	12,325	13.76 (8.53–18.99)	
Brito-Zerón et al,[20] 2017	Spain	12	1239	6.04 (3.43–10.64)	7.6[a]5.5[b]/9922

Follow-up is given as length (either mean or median) with total patient-years. For some studies, only the duration is given.
Abbreviations: NA, not applicable; NG, not given. F, female subjects; M, male subjects.
[a] Mean value.
[b] Median value.
Data from Refs.[4–6,16,20,27,29,30,32,37,41,44,124–126]

leukopenia.[45] Quartuccio and colleagues[45] performed univariate and multivariate analyses on 342 pSS patients. In the 2 groups that were compared, 342 patients were positive for both the histopathology (focal lymphocytic sialadenitis with a focus score of >1 per 4 mm^2) and for anti-Ro and/or anti-La, and 206 patients were positive for with a focus score less than 1 but negative for autoantibodies.

Cryoglobulin-related markers, such as serum cryoglobulins, C3 and C4 complement factors, and serum monoclonal immunoglobulins, are considered substantial predictors of lymphoma development in patients with pSS.[10] C4 hypocomplementemia, more so than C3 hypocomplementemia, is independently associated with the development of lymphoma,[39] poor survival, morbidity such as sialadenitis, and arthritis.[46,47] Low C4 also is associated with an elevated mortality risk (hazard ratio [HR] 2.82; 95% CI, 1.73–4.58; $P<.001$).[48] There also is an association between low complement levels and clinical features, such as fever, cutaneous vasculitis, and cryoglobulinemia.[46] Sicca did not correlate with the development of lymphoma.[27,38,49] In addition, hydroxychloroquine use was not associated with cancer risk in patients with pSS nor was hydroxychloroquine associated with any protective effect on the risk of lymphoma.[50]

The alliance between pSS and intracranial malignant lymphoma remains ambiguous. Nonetheless, despite being rare, MALT lymphoma should be considered a differential diagnosis of a central nervous system mass in the pSS population and in patients with a prior treated tumor because pseudoprogression and radionecrosis must be differentiated from the tumoral development.[51] Lesions due to inflammation, demyelination, infection, or vasculitis can manifest as intracranial masses that are pseudotumoral in nature. Pseudotumoral lesions are important to identify because treatment decision and ultimately disease course are impacted. There are a few case reports of pseudotumor secondary to pSS.[52–55]

MALT lymphoma of the central nervous system is uncommon and can occur in part associated with autoimmune diseases or inflammatory sequela.[56–58] By nature, this lymphoma is indolent and treated with excision and radiotherapy. Pathologically, central nervous system MALT lymphoma is characterized by an extranodal lymphoma composed of a proliferation of centrocyte-like cells and plasmacytoid cells with lymph follicle formation resembling chronic inflammation.[57] There have been reports of intracranial primary MALT lymphoma in SS.[59,60] One such report documents the development of such lesions in the cerebellopontine angle in a female pSS patient. The tumor demonstrated inflammatory features of reactive lymphocytic infiltration with follicle formation, with slightly atypical lymphocytes and plasmacytes with diffuse dense sheets of B cells evidenced by CD20 immunostaining. These cells invaded reactive follicles, showing follicular colonization, and demonstrated aberrant expression of CD43. This all supported the diagnosis of lymphoma.[57]

MALT lymphomas involving the breast are uncommon (<0.5% of all breast malignancies). This is due to the lack of MALT in the breast. Belfeki and colleagues[61] described an unusual mammary MALT lymphoma with amyloid light chain (AL) amyloidosis in the setting of SS. Breast MALT lymphoma is reported in 1.7% to 2.2% of extranodal breast lymphoma.[62]

Cutaneous vasculitis is more frequent in pSS with non-Hodgkin lymphoma (NHL) than in the general pSS population.[63] MALT lymphomas are known to be associated with localized peritumoral amyloidosis in internal organs. It is postulated that AL-type localized nodular cutaneous amyloidosis is a manifestation of MALT lymphoma of the skin.[64] The clinical phenotype and course reflect those of primary cutaneous marginal zone lymphoma. The lymphoplasmacytic variant is now included among the larger group of extranodal B-cell lymphomas of MALT.[64]

OTHER LYMPHOMAS AND LEUKEMIAS

In addition to elevated risk of NHL in pSS (standardized incidence ratio [SIR] 11.5; 95% CI, 8.4–15.4),[49] several studies have suggested that pSS is associated with a higher risk for developing Hodgkin lymphoma.[20,65] Brito-Zerón and colleagues[20] formed the Autoimmune Diseases Study Group (GEAS) that collected a large series of Spanish patients with pSS. Among 1300 consecutive patients who fulfilled the 2002 classification criteria for pSS, 4 pSS patients had Hodgkin lymphoma (SIR 19.41; 95% CI, 7.29–51.72). The control group consisted of sex-specific and age-specific incidence rates of cancer for Spain and were estimated from national mortality data from 2012 by modeling, using a set of age-specific, sex-specific, and site-specific incidence. Mortality ratios were obtained by the aggregation of recorded data from 12 Spanish cancer registries. For Hodgkin lymphoma, mortality ratios for pSS compared with the Spanish controls were 2.6 for men and 2.2 women (age-standardized rates, per 100,000).[20] Although rare, T-cell cutaneous involvement is not completely unheard of in pSS.[66,67] Nonetheless, a majority of T-cell lymphomas associated with SS are angioimmunoblastic T-cell lymphomas.[68] Difficult to diagnose pleomorphic T-cell lymphoma also has been reported in pSS.[67]

T-cell (CD3þ) large granular lymphocyte (LGL) leukemia has been described as associated with pSS.[69] In this study, all patients at a single medical center with LGL leukemia were evaluated for pSS. Among 48 of these patients, 21 had sicca and 13 (27%) had pSS. No patient was diagnosed with pSS prior to the evaluation performed in this study. Thus, sicca as well as pSS are common among patients with LGL leukemia but the prevalence of this leukemia among a cohort of pSS patients and the relative risk for LGL leukemia in pSS are unknown.

The inclination for pSS-related lymphoma to target the parotid glands is supported by several studies.[70–72] In a conducted pooled analysis of 12 case-control studies, including 29,423 participants, SS was found associated with a 1000-fold increase in the risk of parotid gland marginal zone lymphoma and a 6.5-fold increase in the risk of NHL overall.[23]

MULTIPLE MYELOMA

Multiple myeloma is found in excess among cohorts of pSS (**Table 2**). In particular, monoclonal gammopathy in patients with pSS is reported to carry an elevated risk of developing multiple myeloma compared with pSS patients without this finding,[73] but this risk compared with the general population with monoclonal gammopathy is unknown. A recent study from Scandinavia followed 1009 pSS patients for an average of 10 years.[74] Four were diagnosed with multiple myeloma. Each pSS subject had 10 age-specific, sex-specific and residency-matched controls, among whom there were 14 diagnoses of multiple myeloma. All pSS patients with multiple myeloma had anti-Ro and 3 of the 4 had anti-La (HR 6.2 compared with controls). Both Brom and colleagues[75] and Brito- Zerón and colleagues[20] found increased multiple myeloma when comparing pSS to the general population, with SIRs of 35 to 45. Yang and colleagues[76] found monoclonal gammopathy most frequent among pSS patients compared with other inflammatory rheumatic diseases. These workers suggested screening for monoclonal gammopathy and for multiple myeloma as indicated by the presence of monoclonal gammopathy.[76] The authors conclude, given the high risk, that screening likely is warranted.

LUNG CANCER

The pulmonary manifestations of pSS include an array of airway abnormalities.[77] Pulmonary involvement of SS is now regarded both clinically and histopathologically as a

Table 2
Studies of multiple myeloma in Sjögren syndrome with calculated standardized incidence ratios and the 95% CIs

Reference, Year	Location	Number Tumor/ Cohort		Standardized Incidence Ratio (95% CI)	Follow-up Length/ Patient-Years
Kauppi et al,[125] 1997	Finland	2	676	3.4 (0.4–12.4)	22 (duration)/ 5336
Pertovaara et al,[30] 2001	Finland	1	110	8.3 (0.2–48)	15 (duration)/ 1015
Theander et al,[41] 2006	Sweden	1	286	3.27 (0.08–18.23)	8[b]/2464
Zhang et al,[4] 2010	China	2	1320	37.9 (4.58, 136.7)	4.2[a]/5544
Weng et al,[126] 2012	Taiwan	5	6911	F: 6.09 (1.98, 14.2)	3.5[a]/27,246
Brito-Zerón et al,[20,c] 2017	Spain	31	1239	36.17 (25.44, 51.43)	7.6[a], 5.5[b]/9922

Follow-up is given as length (either mean or median) with total patient-years. F, female subjects only in this study.
[a] Mean value.
[b] Median value.
[c] This study included both multiple myeloma and other immunoproliferative diseases.
Data from Refs.[4,20,30,41,125,126]

wide spectrum of lung lymphoproliferative disorders ranging from benign to malignant. The incidence rate of lung cancer in pSS has been reported to be 0.477%, with similar studies confirming this and supporting the concept that pSS has an increased risk of lung cancer (**Table 3**), with SIR 4.51 compared with the general population's incidence.[4,41,75,78]

In patients with pSS and in the SS group as a whole, there are independent and significant associations between lung cysts and anti-La seropositivity or clonally derived lymphoproliferative disorder. Lung cysts noted on chest CT could serve as a prognostic predictor of clonally derived lymphoproliferative disorder in patients with SS.[79] Another study suggested that lung cancer might be derived from cystic lesions associated with SS.[80] Lung adenocarcinoma has been associated with another entity distinct from cysts, lymphocytic interstitial pneumonitis (LIP) caused by pSS.[81] A small study examining pSS patients with lung cancer noted women were seen more frequently with adenocarcinoma as the most common pathologic type of lung cancer. pSS patients with lung cancer were noted to be significantly older than those who did not develop lung cancer, and immunosuppressant treatment might be associated with lung cancer.[78]

Unusual combinations of lung cancer have occurred in conjunction with SS. Such examples include lung adenocarcinoma in LIP associated with pSS[81] as well as a rare association of pulmonary carcinoid, lymphoma, and SS.[82] Regarding lung adenocarcinoma in LIP, histopathologic diagnosis of nodular lesion revealed papillary adenocarcinoma in LIP with marked mononuclear infiltration adjacent to papillary adenocarcinoma. This infiltrate was composed of mature plasma cells resembling plasma cell interstitial pneumonitis. Although plasma cell interstitial pneumonitis frequently is classified separately from LIP, most investigators believe that it represents a variant of LIP.[81,83] The mechanisms of plasma cell predominance, however, with respect to papillary adenocarcinoma remains to be elucidated. Nonetheless, primary lung tumors should be considered in the differential diagnosis of nodular lesions in patients with LIP associated with pSS.[81]

Table 3
Studies of lung cancer in Sjögren syndrome with calculated standardized incidence ratios and 95% CI

Reference, Year	Location	Number Tumor	/Cohort	Standardized Incidence Ratio (95% CI)	Follow-up Length/ Patient-Years
Theander et al,[41] 2006	Finland	4	286	2.71 (0.74–6.94)	8[b]/2464
Weng et al,[126] 2012	Taiwan	20 9	6911 941	F: 1.40 (0.85–2.16) M: 1.23 (0.56, 2.33)	3.5[a]/27,246
Brito-Zerón et al,[20] 2017	Spain	6	1239	1.29 (0.58, 2.87)	7.6[a], 5.5[b]/9922

Follow-up is given as length (either mean or median) with total patient-years. F, female subects; M, male subjects.
[a] Mean value.
[b] Median value.
Data from Refs.[20,41,126]

Other deposition diseases that can infiltrate lung tissue are seen in conjunction with SS. According to the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, light chain deposition disease (LCDD) belongs to the group of monoclonal immunoglobulin deposition diseases.[84,85] This disease is indolent in nature and can be the first manifestation of a previously undetected plasma cell disorder or low-grade lymphoma with plasma cell differentiation.[86] Localized LCDD is rare and often associated with a B-lymphoproliferative or plasma cell neoplasm.[85,87–92] Nodular pulmonary LCDD (NPLCDD) is uncommon and typically limited to the lung. NPLCDD frequently is seen in association with SS and/or low-grade B cell lymphoproliferative disorder.[85]

THYMUS MASSES

True thymic hyperplasia demonstrates an enlarged but histologically normal tissue, which is cured with excision,[93] whereas thymic lymphoid hyperplasia usually does not show thymic enlargement but an increased number of lymphoid follicles with hyperplastic germinal centers.[93,94] With an abnormal thymus in pSS, the differential diagnosis may include MALT lymphoma, Castleman disease, and lymphocyte predominant thymoma (type B1).[95] Multilocular thymic cysts are thought to be the consequence of cystic transformation of medullary epithelium induced by an acquired inflammatory process.[96] Thymic lesions in pSS primarily consist of extranodal MALT lymphoma and rarely consist of thymoma, thymic carcinoma, or lymphoid hyperplasia.[97] A handful of cases reporting thymic lymphoid hyperplasia associated with pSS have been documented and all were accompanied by multilocular thymic cysts.[97–100] One case report noted a diagnosis of thymic lymphoid hyperplasia with multilocular thymic cysts that subsequently led to a new diagnosis of SS based on sicca symptoms, positive serology, and pathology.[95] Multilocular thymic cysts are rare acquired multicystic lesions generally associated with autoimmune disorders (myasthenia gravis and SLE), tumors (thymoma and lymphoma), and human immunodeficiency virus infection.[101] Uncommonly multilocular thymic cysts have been noted in pSS,[100] although there are no reports of sicca symptoms improving upon thymectomy.[95]

SKIN CANCER

Skin complications of pSS are well established and include xerosis, epidermal IgG deposits, cutaneous vasculitis, and cutaneous B-cell lymphoma. To a lesser degree,

alopecia, vitiligo, and papular lesions also have been attributed to pSS.[63] Regarding malignancy, a recent study has noted that patients with SLE or pSS have a significantly increased risk of nonmelanoma skin cancer. The patients most at risk were those receiving higher cumulative doses of corticosteroids and hydroxychloroquine.[102] An expedited progression of skin malignancy was not reported; however, 1 case report discussed a male pSS patient without mention of immunosuppressive treatment who rapidly developed a succession of cutaneous squamous cell carcinoma skin lesions despite undergoing surgical resection to remove the cutaneous squamous cell carcinoma on 3 separate occasions.[103]

OTHER CANCERS, INCLUDING BREAST

A summary of studies of nonlymphoma cancers among SS is given in Supplemental Table 2. Other nonlymphoid cancers, including breast cancer, also can occur in SS patients; however, an increase in the incidence of these cancers has not been demonstrated in every study.[5,75] SS has been associated with a statistically significantly reduced risk of breast cancer in a Swedish study[104]; however, another study found no difference in risk for pSS subjects compared with the general population.[105] Hemminki and colleagues[104] studied breast, uterine, and ovarian cancers among 200,000 subjects with 1 of 33 autoimmune diseases. The SIR for breast cancer among pSS patients was only 0.49; meanwhile, the HR for endometrial cancer was increased approximately 4-fold. In another large study of 209,929 US patients with breast cancer at greater than 66 years of age, however, there was no association with pSS compared with age-matched and sex-matched controls from the same database. A recent study of an Argentinian pSS cohort (n = 157) showed increased SIRs for tongue, breast, uterus, and lung cancers. Historical population controls were used as a comparison group.[75] Although an association between pSS and thyroid cancer might exist, further investigations are needed.[106] A study from China of 1320 pSS patients used historical population controls and found an increased SIR for thyroid cancer. There was 1 thyroid cancer, however, among the pSS patients. Furthermore, pSS patients likely undergo a radiological and physical examination of the neck at a much greater rate than the general population. Thus, the data are mixed and confounded concerning an association of pSS to carcinoma. The differences in these studies may be due to methodology. For instance, the use of historical population controls instead of a contemporaneous control group. In addition, ethnic differences could be important.

Diagnosis of breast cancer can be a challenge in pSS. Localized amyloidosis should be suspected in patients with consistently high serologic activity and suggestive lesions[107] because amyloid tumor of the breast has been reported in pSS, which may be suggestive of breast cancer. If nonstructural substances are noted with hematoxylin-eosin staining, Congo red staining should be added.[108] Physicians should keep in mind the possibility of overstaged breast cancer due to misinterpretation of axillary metastasis in patients with SS presenting with a breast mass. It is wise to obtain axillary node status first to correctly establish tumor stage situation of SS patient with breast cancer.[109]

In patients with pSS and a history of rapidly developing neck lymphadenopathy, potential malignancies other than lymphoma should be entertained. This includes involvement of the nasopharynx.[110] In such an instance, a biopsy of the nasopharynx is necessary to make a definitive diagnosis. The coexistence of SS with nasopharyngeal carcinoma (NPC), however, rarely has been reported.[111] Nonetheless, with pSS and NPC, significantly elevated antibody titers for Epstein-Barr virus viral capsid antigen and early antigen can be found.[111] Both pSS and NPC are related to previous Epstein-Barr virus

infection.[112,113] Reduced radiation dose may need to be considered to lessen the risk of developing cranial nerve palsy in patients with pSS and head/neck carcinoma.[111]

Other areas in the head and neck region possibly are involved in an association of pSS with cancer, but diagnoses other than cancer may be found for a mass in this region. A patient with an eyelid mass subsequently was diagnosed with both pSS and localized amyloidosis of the lacrimal gland.[114] There is a report of 64-year-old woman diagnosed with pseudolymphoma of the lacrimal gland and pSS.[115] An Argentinian study of cancer in pSS found an SIR for tongue cancer approximately 50 times that found in a matched general population, but there was only 1 pSS with tongue cancer.[75] Nonetheless, tongue cancer might be increased but still uncommon among pSS patients.

Vaginal dryness can be attributed to SS. Despite a higher prevalence of dyspareunia and vaginal dryness in SS patients, no significant differences were observed between SS and the control group who were evaluated by using cervical cytology, colposcopy examination, and human papillomavirus DNA tests.[116] These data suggest that cervical cancer is not increased among pSS patients.

SARCOMA

Parotid liposarcomas have been reported rarely in adults. There has only been 1 known association with SS and parotid liposarcoma.[117] Thus, with only a single report, the authors conclude that there is no association between parotid sarcoma and pSS.

Angioimmunoblastic lymphadenopathy is a rare lymphoproliferative disorder marked by the clinical features of lymphadenopathy, hepatosplenomegaly, rash, and hypergammaglobulinemia.[118] A case report describing a patient with immunoblastic lymphadenopathy and features of SS and SLE has been reported. Clinical features included sicca syndrome, enlarged parotids, generalized lymphadenopathy, rash, alopecia, and synovitis, with positive serology (positive antinuclear antibody test, double-stranded DNA, and positive lupus band test) and hemolytic anemia. At autopsy, immunoblastic sarcoma was found that had invaded the myocardium, which stained for both κ and λ light chains by immunoperoxidase techniques.[119]

CANCER THERAPY AND SJÖGREN SYNDROME

Immunotherapy for cancer produces autoimmune disease, and the development of autoimmunity is associated with the responsiveness of the cancer. Generally organ-specific autoimmune disease, however, has been reported.[120–122] One case concerned a long-term survivor with metastatic colon carcinoma with node and lung metastases, who developed clinical, pathologic, and immunologic SS during maintenance treatment with low-dose subcutaneous metronomic interleukin (IL)-2 and granulocyte-macrophage colony-stimulating factor, which is part of GOLFIG treatment. Her symptoms of keratoconjunctivitis and sicca remained stable until the end of the maintenance treatment with IL-2 and disappeared completely a few weeks later. This case shows a possible correlation between the efficacy of treatment, long-term survival, and the occurrence of autoimmunity in a patient who received chemoimmunotherapy regimen.[123]

SUMMARY

Clinicians should closely pay attention to the possibilities of the various cancers in pSS patients. Currently recommended screening testing based on age and sex should be pursued. Cancer screening for patients with pSS should focus on NHL and multiple myeloma.[4] Skin cancer should be considered increased among pSS patients, such that thorough cancer-associated examinations with skin biopsy when appropriate

should be routine. Respiratory symptoms should prompt a thorough history and physical examination. Furthermore, chest CT scanning is important for the diagnosis and assessment of lung cancer in pSS patients. Clinical stages and individualized treatments for pSS patients with possible cancer should be determined carefully.

CLINICS CARE POINTS

- There is a high risk of lymphoma, especially MALT-associated disease.
- Lymphoma most commonly affects parotid gland.
- Multiple myeloma occurs more commonly in SS. Patients should be screened for monoclonal gammopathy.
- Diagnosis and staging of breast cancer may be difficult in SS.
- Lung cancer is 5 times more frequent in SS.
- Lung cancer is associated with lung cysts.

DISCLOSURE

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SUPPLEMENTAL TABLE 1: COMPARISON OF STANDARDIZED INCIDENCE RATIOS FOR OVERALL MALIGNANCY INCIDENCE IN PATIENTS WITH SJÖGREN SYNDROME

Author, Year	Country	Standardized Incidence Ratio (95% CI)	Malignancy (no.)	Total Number of Patients	Follow-up Time (Person- Year)
Kassan et al,[124] 1978 Only women	USA	2.2	15	142	8.1 (mean) 22 (duration) (1099)
Thomas et al,[127] 2000	Scotland	M: 0.66 (0.21, 1.54) F: 1.36 (0.98, 1.83)	M: 5 43	M: 106 F: 576	5.3 (mean) (652,133)
Pertovaara et al,[30] 2001	Finland	1.1 (0.5–2.2)	8	110	15 (duration) (1015)
Zhang et al,[4] 2010	China	3.25 (2.12, 4.52)	29	1320	4.2 (mean) (5544)
Lazarus et al,[5] 2006	Britain	2.63 (1.73, 3.99)	25	112	10.8 (mean) (1210)
Theander et al,[41] 2006	Sweden	1.42 (0.98–2.00)	33	286	8 (median) (2464)
Weng et al,[126] 2012	Taiwan	1.04 (0.91–1.18)	277	7852	3.5 (mean) (27,246)
Liang et al,[6] 2014 (up to 12/2013	Multiple	1.53 (1.17–1.88		11,889 (from 8 studies)	
Brito-Zerón et al,[20] 2017	Spain	1.91 (1.59–2.27	121	1239	7.6 (mean) 5.5 (median) (9922)

Data from Refs.[4–6,20,30,41,124,126,127]

SUPPLEMENTAL TABLE 2: STUDIES OF NONLYMPHOMA MALIGNANCY IN SJÖGREN SYNDROME

Cancer Type	Study, Year	Country	Standardized Incidence Ratio (95% CI)	Cancer Patients (no.)	Total Patients (no.)	Follow-up Time, (Person-Year)
Non-Hodgkin lymphoma	Lazarus et al,[5] 2006	Britain	1.53 (0.89–2.63)	13	112	8 (median) (2464)
Hodgkin lymphoma	Brito-Zerón et al,[20] 2017	Spain	19.41 (7.29–51.72)	4	1239	7.6 (mean) 5.5 (median) (9922)

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Cancer Type	Study, Year	Country	Standardized Incidence Ratio (95% CI)	Cancer Patients (no.)	Total Patients (no.)	Follow-up Time, (Person-Year)
Multiple myeloma	Kauppi et al,[125] 1997	Finland	3.4 (0.4–12.4)	2	676	22 (duration) (5336)
	Pertovaara et al,[30] 2001	Finland	8.3 (0.2–48)	1	110	15 (duration) (1015)
	Theander et al,[41] 2006	Sweden	3.27 (0.08–18.23	1	286	8 (median) (2464)
	Zhang et al,[4] 2010	China	37.9 (4.58, 136.7)	2	1320	4.2 (mean) (5544)
	Weng et al,[126] 2012	Taiwan	F: 6.09 (1.98–14.2)	5	6911	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017 (multiple myeloma and immunop-roliferative disease)	Spain	36.17 (25.44–51.43)	31	1239	7.6 (mean) 5.5 (median) (9922)
Solid tumors	Kauppi et al,[125] 1997	Finland	1.1 (0.8–1.5)	41	676	22 (duration) (5336)
	Zhang et al,[4] 2010	China	2.12 (1.27, 3.31)	19	1320	4.2 (mean) (5544)
	Brito-Zerón et al,[20] 2017	Spain	1.13 (0.88–1.46)	60	1239	7.6 (mean) 5.5 (median) (9922)
Leukemia	Kauppi et al,[125] 1997	Finland	3.6(0.8–10.6)	3	676	22 (duration) (5336)
	Brito-Zerón et al,[20] 2017	Spain	2.02 (0.65, 6.26)	3	1239	7.6 (mean) 5.5 (median) (9922)
Gastroin-testinal	Theander et al,[41] 2006	Finland	1.75 (0.76–3.46)	8	286	8 (median) (2464)
	Weng et al,[126] 2012	Taiwan	F: 1.56 (0.75, 2.86)	10	6911	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017 (stomach)	Spain	F: 2.53 (1.05, 6.07)	5	1145	7.6 (mean) 5.5 (median) (9922)

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Cancer Type	Study, Year	Country	Standardized Incidence Ratio (95% CI)	Cancer Patients (no.)	Total Patients (no.)	Follow-up Time, (Person-Year)
Colon	Weng et al,[126] 2012	Taiwan	F: 0.22 (0.05–0.65)	3	6911	3.5 (mean) (27,246)
	Landgren et al,[128] 2012	USA (VA)	0.99 (0.55, 1.79)	12	7349	7.47 (mean)
	Brito-Zerón et al,[20] 2017	Spain	0.89 (0.46, 1.72)	9	1239	7.6 (Mean) 5.5 (median) (9922)
Breast	Theander et al,[41] 2006	Finland	0.51 (0.10–1.48)	3	286	8 (median) (2464)
	Hemminki et al,[104] 2012	Sweden	0.46 (0.26, 0.75)	16	1516	(16,700)
	Weng et al,[126] 2012	Taiwan	0.99 (0.70, 1.36)	37	6911	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017	Spain	0.89 (0.53, 1.51)	14	1239	7.6 (mean) 5.5 (median) (9922)
Cervical cancer	Hemminki et al,[104] 2012	Sweden	0.83 (0.08–3.06)	2	1516	(16,700)
	Weng et al,[126] 2012	Taiwan	0.65 (0.26–1.34)	7	6911	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017	Spain	0.72 (0.1, 5.1)	1	1239	7.6 (mean) 5.5 (median) (9922)
Mouth and throat	Theander et al,[41] 2006	Finland	3.03 (0.08–16.88)	1	286	8 (median) (2464)
	Weng et al,[126] 2012	Taiwan	F: 1.42 (0.29, 4.16)	3	6911	3.5 (mean) (27,246)
	Landgren et al,[128] 2012	USA	1.41 (0.90, 2.22)	20	7349	7.47 (mean)
	Brito-Zerón et al,[20] 2017	Spain	F: 4.81 (1.81–12.83)	4	1145	7.6 (mean) 5.5 (median) (9922)
Thyroid	Theander et al,[41] 2006	Finland	6.86 (0.17–38.21)	1	286	8 (median) (2464)
	Weng et al,[126] 2012	Taiwan	F: 2.56 (1.40, 4.30)	14	6911	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017	Spain	F: 5.17 (1.94–13.79)	4	1145	7.6 (Mean) 5.5 (median) (9922)

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Cancer Type	Study, Year	Country	Standardized Incidence Ratio (95% CI)	Cancer Patients (no.)	Total Patients (no.)	Follow-up Time, (Person-Year)
Lung	Theander et al,[41] 2006	Finland	2.71 (0.74–6.94)	4	286	8 (median) (2464)
	Weng et al,[126] 2012	Taiwan	F: 1.40 (0.85–2.16) M: 1.23 (0.56, 2.33)	20 9	6911 941	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017	Spain	1.29 (0.58, 2.87)	6	1239	7.6 (mean) 5.5 (median) (9922)
Nonmelanoma skin cancer	Theander et al,[41] 2006	Finland	1.93 (0.23–6.98)	2	286	8 (median) (2464)
	Weng et al,[126] 2012	Taiwan	F: 1.56 (0.42–3.99)	4	6911	3.5 (mean) (27,246)
Melanoma of the skin	Brito-Zerón et al,[20] 2017	Spain	1.16 (0.29, 4.62)	2	1239	7.6 (mean) 5.5 (median) (9922)
Kidney and urinary tract	Theander et al,[41] 2006	Finland	0.77 (0.02–4.29)	1	286	8 (median) (2464)
	Weng et al,[126] 2012	Taiwan	F: 1.18 (0.38–2.76)	5	6911	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017	Spain	1.8 (0.58, 5.57)	3	1239	7.6 (mean) 5.5 (median) (9922)
Bladder	Weng et al,[126] 2012	Taiwan	1.77 (0.65–3.84)	6	6911	3.5 (mean) (27,246)
	Brito-Zerón et al,[20] 2017	Spain	0.95 (0.24, 3.8)	2	1239	7.6 (mean) 5.5 (median) (9922)

Data from Refs.[4–6,20,30,41,104,125,126,128]