Review paper

Reumatologia 2017; 55, 3: 136–139
DOI: https://doi.org/10.5114/reum.2017.68913

Is primary Sjögren's syndrome a risk factor for malignancies different from lymphomas? What does the literature highlight about it?

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Abstract

Background: Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease with an elevated risk of developing lymphoproliferative malignancies (LM). Whether pSS is a risk factor or not for non-lymphoma malignancies (NLM) has been scarcely evaluated in the literature. Age is per se a risk factor for malignancies: patients over 70 years old have 4 times higher risk for cancers than adults. Even if the mean age of pSS onset usually is in the 4th and 5th decade, its onset in patients aged over 65 years (Elderly Onset pSS – EOpSS) is not uncommon.
Material and methods: To evaluate pSS as a risk factor for NLM we performed a systematic electronic search on PubMed in the period 2006–2016 to identify all the publications on this topic. The studies were eligible for inclusion if they reported specific Standardized Incidence Ratio (SIR) with 95% CI. Studies that did not report sufficient published and/or original data were excluded.
Results: Only 7 articles of 494 that we found in PubMed fulfilled the inclusion criterion. In the vast majority of these, SIR values were not statistically significant for NLM. The occurrence of NLM after LM was statistically significant in some studies and a NLM represented the most frequent cause of death. The possibility that NLM may represent a paraneoplastic syndrome seems much more frequent than LM, the risk of which increases with time after the diagnosis. Data regarding the neoplastic weight of EOpSS are mainly pointed out by case reports.
Conclusions: Primary Sjögren's syndrome is not associated with an increased risk for NLM. However the possibility that NLM may appear after recovery from lymphoma should be carefully considered because it could be cause of the patient's death. Similarly the possibility that NLM may represent a paraneoplastic syndrome must be highlighted. The relationship between EOpSS and SIRs for NLM should be deepened with studies on ad hoc cohorts.

Key words: systematic review, cancer risk, primary Sjögren's syndrome, non lymphomas malignancies.

Background

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by a progressive lymphocytic infiltration of the exocrine glands, mainly salivary and lachrymal glands causing xerostomia and xerophthalmia as in the 19 cases described by Sjögren in 1933 [1]. When SS occurs in the absence of any other diseases, the diagnosis of primary SS (pSS) can be made [2]. In addition to the involvement of the exocrine glands, SS can induce a wide variety of systemic and extraglandular manifestations with different clinical pictures and prognostic consequences. A systemic disease activity index for SS named EULAR Sjögren's syndrome disease activity index (ESSDAI) has been proposed since 2010; it has been validated and

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Submitted: 1.04.2017; **Accepted:** 12.06.2017

used in most clinical studies [3, 4]. In 20–40% of patients with SS, severe clinical manifestations are present involving multiple organ systems with an high ESSDAI score [5]. Even if the mean age of pSS onset usually is in the 4th and 5th decade, its onset in patients aged over 65 years old is not uncommon [6–10]. In particular, in a Norwegian study, individuals aged 71–74 years had a prevalence rate of pSS 6.3–8.07 higher than those aged 40–44 years [7].

In patients with pSS the high incidence of lymphoma was firstly reported by Bunim and Talal in 1963 [11] and has been confirmed more and more since then [12–15]. The related risk for non-Hodgkin's lymphoma (NHL) and mucosa- associated lymphoid tissue (MALT) NHL is generally estimated at 10 to 15 times when compared to the general population but in some studies the standardized incidence ratios (SIRs) were > 30 until 48.1 [16–18]. In recent years, several predictors of lymphoma development have been identified [19]. The importance of ESSDAI score has been also confirmed in recent times: patients with a higher ESSDAI score have a higher risk for lymphoma development [20]. On the other hand, the relationship between pSS and risk for malignancies different from lymphomas is still unclear. Age itself is a risk factor for malignancies: in elderly patients, aged over 70 years, cancer risk may be 40 times higher than in young people and 4 times than in adults (40–59 years old). It is estimated that in 2020, in population aged over 65 years, the percentage of patients with a diagnosis of cancer will exceed 70% [21]. Therefore, the relationship between elderly onset of pSS (EOpSS) and malignancy risk has a particular value.

Aim: to evaluate pSS (also as EOpSS) as a risk factor for development of non-lymphoma malignancies (NLM), considering as inclusion and eligible criterion this specific Standardized Incidence Ratio (SIR) with 95% CI [22].

Methods

A systematic search of scientific literature on PubMed in the period September 2006–January 26, 2017 has been performed using the following key words: primary Sjögren syndrome, cancer risk, autoimmune diseases, elderly, carcinogenesis, malignancy. The studies did not report the inclusion criterion have been excluded; likewise, the studies that did not report sufficient published data and those ones that did not report original data (reviews or comments, for example). Case reports and case series have been also included.

Results

A total of 494 non-overlapping citations were identified through PubMed database (see *S1 – supplementary file*). 462 citations were excluded on screening of abstracts or titles with general criteria leaving 32 articles for the full-text review and assessment for eligibility (see *S2 – supplementary file*). Twenty-five of these articles were excluded: 20 had no enough data to calculate SIRs with 95% CI; 5 were review articles or comments. In the end, only seven articles were eligible for this review (Fig. 1). They are mostly retrospective and case-control studies on database. Table I shows the main results of these studies.

In two studies, SIRs were calculated on overall cancer risk [23, 24]: it is reasonable to suppose that the SIRs, considering only NLM, would be even smaller. Among 450 patients with pSS monitored at the University Hospital of Ioannina in Greece, none developed NLM in more than 33 years [25]. An age over 65 years – with a specific reference in the study – was not associated with an increased cancer risk [16, 18, 23, 25, 26]. A recent meta-analysis by Liang et al. [27] highlighted that the number of studies exploring the association of pSS with the risk of NLM was so small that meta-analysis on subgroup was not possible [27]. When evaluated, the promoting role of immunosuppressive or biotechnologic drugs was almost constantly excluded. Some case reports found pSS associated with different types of malignancies. In some cases, the sicca syndrome represented a local condition promoting particular types of neoplasias such as cancer of tongue or nasopharyngeal carcinoma [16, 28].

Discussion

In the studies published between 2006 and 2016, SIR values were not statistically significant for NLM in patients with pSS. Some points must be highlighted. Some studies used hospital registries and it was possible that the subsequent evaluations could regard patients with more severe form of pSS. As well-known, an important

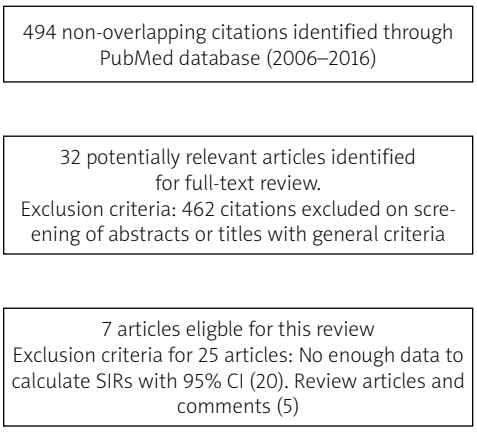

Fig. 1. Flow chart showing article identification, inclusion and exclusion.

Table I. No-lymphoma malignancies risk in pSS

Authors	Year of publication	Study design	Cohort	Database	pSS (number)	SIR
Lazarus et al. [18]	2006	retrospective	outpatient department	Thames Cancer Registry	112	1.5
Theander et al. [26]	2006	retrospective	population-based	Swedish Cancer Register	286	1.42
Gadalla et al. [35]	2009	retrospective	Medicare data	Medicare data (only breast cancer)	196	1.01
Zhang et al. [16]	2010	retrospective	hospitalized patients	Peking Union Medical College Hospital	1320	2.12
Weng et al. [24]	2012	retrospective	population-based	National Health Insurance, Taiwan	7852	1.04
Boussios et al. [25]	2014	retrospective	hospitalized patients	Rheumatology Department	450	0
Yu et al. [34]	2016	retrospective	population-based	National Health Insurance Research Database, Taiwan	11988	1.19

involvement of multiple organ systems is only recognized in 20–40% of patients with pSS; these patients have an higher ESSDAI score. In this regard the lack of data in outpatients could be significant. On the other hand, even in the studies based on hospital registries or general databases ESSDAI score was never evaluated as specific point and so the relationship between ESSDAI score and NLM risk could remain only speculative.

Although pSS has a high incidence of benign monoclonal gammopathy [29], multiple myeloma (MM) is very rare [30, 31]. The presence of a benign monoclonal gammopathy can realize a risk of MM even higher than the lymphoma's one as recently reported in a small casuistry [32]. Some patients with pSS and lymphoma can develop an additional cancer, for example a renal or lung carcinoma [18, 23]. This additional cancer can onset several years after the diagnosis of lymphoma and even after its complete remission. Defective DNA-repair mechanisms could have a pathogenetic role [33]. In several cases, this second neoplasia was the cause of the patient's death [18, 23]. Furthermore SIRs for NLM can be higher in the first year after diagnosis of pSS than in subsequent years [16, 18, 23]. On the other hand, the risk of lymphoma increased with time after the diagnosis of pSS [23, 26]. The number of patient/years was scarcely (or not) evaluated in the seven publications we considered in Table I and this point represented another significant limit. The vast majority of the patients were Chinese [16, 24, 33] and these data could suggest that genetic and local environmental factors could have an effect on cancer risk but when SIRs have been evaluated in non-Chinese databases and cohorts [18, 25, 26, 34], they were not statistically different.

Finally, even if EOpSS is not uncommon and age itself is one of the most important elements for development of malignancies, data regarding the neoplastic weight of EOpSS are very scarce and mainly pointed out by case reports. One study evaluated the incidence and SIR of breast cancer in a cohort of elderly patients with some chronic autoimmune diseases and did not find an increased risk in the group of patients with EOpSS [35].

Conclusions

As highlighted in previous review articles, the overall incidence of malignancies in patients with pSS is almost entirely due to the high incidence of lymphomas.

New (and non-retrospective) studies are required to address a series of questions that have only theoretical and/or partial answers to date:

We did not find studies on the relationship between ESSDAI scores and NLM. All the studies were based on hospital databases and hence it is possible that they considered patients with severe clinical pictures of pSS. From a speculative point of view, it is possible that in patients with mild pSS (or in overall pSS patients) the SIRs for non-lymphoma development could be even smaller.

The paraneoplastic meaning of pSS remains poorly studied but some data highlighted the possibility that this link between NLM and pSS could be more important than that between pSS and lymphoma whose risk increases with time after the diagnosis.

The relationship between EOpSS and SIRs for NLM development must be deepened with more studies on *ad hoc* cohorts. In a word that is aging, this specific point can be of great value.

The risk to develop a NLM in a patient with pSS healed by a LM deserves a more in-depth assessment for the understandable repercussions on public health choices.

The authors declare no conflict of interest.

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