SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Rheumatology

Sjögren's Syndrome: Emergence of a New Paraneoplastic Syndrome? About 5 Cases

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DOI: 10.36347/sasjm.2023.v09i02.013 | **Received:** 07.01.2023 | **Accepted:** 13.02.2023 | **Published:** 18.02.2023

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Abstract **Original Research Article**

Introduction: Gougerot-Sjögren's syndrome (GSS) is a systemic autoimmune disease with malignant transformation to non-Hodgkin's lymphoma (NHL) as its most formidable complication. There are few associations described in the literature with other solid tumours. We report 5 cases of SGS associated with solid tumours. ***Methodology:*** This was a retrospective, descriptive study conducted in the Rheumatology Department of the Aristide Le Dantec University Hospital in Dakar from January 2006 to December 2020. ***Results:*** Over the period we collected 5 cases. They were divided into 3 men and 2 women with a mean age of 73.4 years (51-83 years). The average diagnostic delay was 158.4 months or 13 years (120-240 months). The tumour occurred during the evolution of the GSS in 3 cases while the GSS occurred during the evolution of the tumour in 2 cases. The associated tumours were prostate cancer in 3 cases, ovarian cancer in 2 cases and colon cancer in 1 case. Paraneoplastic hyperuricaemia was present in 2 patients. The evolution was marked by death in 2 patients. ***Conclusion:*** We report in our study 5 observations of SGS associated with solid tumors.

Keywords: Gougerot-Sjogren's syndrome, adenocarcinoma, solid tumour

INTRODUCTION

Sjögren's syndrome is a systemic autoimmune disease characterised by lymphocytic infiltration of the exocrine glands (epithelitis) with tropism in the salivary glands, lacrimal glands, vaginal glands in women, and the upper respiratory tract [1, 2]. Gougerot-Sjögren's syndrome (GSS) is most common in women (sex ratio 9:1) with an average age of 50 years [3]. Glandular manifestations are the most suggestive, such as lacrimal, salivary and vulvovaginal involvement. Other extraglandular manifestations may occur, notably articular, nervous, digestive, renal and pulmonary. The most serious complication is malignant transformation into non-Hodgkin's lymphoma (NHL). The standardised incidence ratio (SIR) has been estimated between 44 and 5 depending on the study [2]. Nevertheless, few studies investigating associations with other cancers, including solid organ tumours (colon, liver, ovary, breast), have been reported in patients with primary Sjogren's syndrome (PSS) [4-10]. We report 5 observations of the association between SSp and adenocarcinoma.

PATIENTS AND METHOD

This was a retrospective, descriptive study carried out in the Rheumatology Department of the CHU Aristide Le Dantec of Dakar from January 2006 to December 2020. The patients included were those with a combination of solid cancer and primary Sjögren's syndrome. Patients with unexplainable data and those without histopathological findings of solid cancer were excluded. Sjögren's syndrome was retained on the basis of epidemiological, clinical and paraclinical arguments supported by the ACR/EULAR 2016 classification criteria. The diagnosis of solid cancer was based on clinical, paraclinical and pathological evidence. Data were analysed using SPSS version 25.0.

RESULTS

In total we had 5 observations of the association between SSp and solid cancer. They were divided into 3 men and 2 women with a mean age of 73.4 years with extremes of 51 and 83 years. The mean diagnostic delay was 158.4 months (13 years) with extremes of 120 months and 240 months. The tumour occurred during the evolution of the pSS in 3 cases while the pSS occurred during the evolution of the

tumour in 2 cases (Table I). The average diagnostic interval between the two diseases was 112.8 months (9.4 years) with extremes of 48 months and 144 months. The clinical and paraclinical manifestations are listed in Table II. There was an alteration of the general condition in 50% of the cases. Polyarthritis was present in 80% of cases. The dry syndrome was present in all patients. Signs related to the solid tumour were noted, in particular tumour syndrome, portal hypertension syndrome and chronic diarrhoea in 20% of cases respectively.

Paraclinically, the inflammatory syndrome was present in 60% of cases. Antinuclear antibodies and anti ECT were positive in 50 and 25% of cases respectively. PSA was positive in 60% of cases. On imaging, metastases were observed in 3 patients. The metastases were hepatic (50% of cases), peritoneal (50%), splenic (25%) and pulmonary (25%). Accessory salivary gland biopsy (ASGB) was pathological in 100% of cases.

The tumours found were prostate cancer in 3 cases, ovarian cancer in 2 cases and colon cancer in 1 case (Table III). The associated pathologies were mainly diabetes and metabolic syndrome (Table IV). Paraneoplastic hyperuricaemia was present in 2 patients.

The treatment instituted was based on methotrexate, hydroxychloroquine and corticoids for SSp and chemotherapy and surgery for cancers (Table V). The evolution was unfavourable and marked by death in 2 patients.

Table I: Circumstances of discovery of the association

Circumstances of discovery	Frequency	Percentage in %
Manifestations of Sjögren's	2	40,0
Tumour manifestations	3	60,0
Total	5	100,0

Table II: Clinical and paraclinical manifestations of the association

Clinic	Variables	Workforce (Percentage %)
General condition	Altered general condition	2 (40)
Joint signs	Polyarthritis	4 (80)
	Oligoarthritis	1 (20)
Extra-articular signs	Dry syndrome	5 (100)
	Bone pain	0 (100)
	Tumour syndrome	1 (20)
	Microadenopathies	1 (20)
	Portal hypertension syndrome	1 (20)
	Chronic diarrhoea	1 (20)
Paraclinical		
Biology	Inflammatory syndrome	3 (60)
Immunology	PSA pathologie (n=3)	3 (100)
	Antinuclear antibodies	2 (50)
	Anti ECT antibodies	1 (25)
Imaging	Liver metastases	2 (50)
	Splenic metastases	1 (25)
	Peritoneal metastases	2 (50)
	Lung metastases	1 (25)
Anatomopathology	BGSA pathological (grade ≥3)	4 (100)

Table III: Etiology of tumours

Etiologies	Frequency	Percentage in %
Ovarian cancer	1	20
Prostate cancer	3	60
Colon cancer	1	20

Table IV: Associated pathologies

Associated diseases	Frequency	Percentage in %
Diabetes	2	40
Metabolic syndrome	1	20
Gastrodudodenal ulcer	1	20
Obesity	1	20
AOMI+cardiomyopathy+discarthrosis	1	20

Table V: Treatment

Treatment	Frequency	Percentage in %
Methotrexate	4	80
Hydroxychloroquine	4	80
Biphosphonate	3	60
Corticoïd	1	20
Chemotherapy	2	40
Hormonotherapy	3	60
Surgery	1	20

DISCUSSION

We report 5 cases of SSp associated with solid tumours, including 3 men and 2 women with a mean age of 73 years. In the literature, SSp has been most frequently associated with NHL. This association is explained pathophysiologically by several etiopathogenic steps. The first step is the chronic stimulation of polyclonal B lymphocytes (LB), especially in patients with rheumatoid factor. This association is at the origin of the increased risk of oncogenic mutation and monoclonal selection. Other mechanisms have been suggested, such as checkpoint dysfunction at the origin of LB activation, mutation of the germinal ectopic centre of TNFAIP3 (which controls NF-kb), which would accelerate the development of the haemopathy [11]. The factors at the origin of carcinomatous transformation are not yet identified to our knowledge [12].

However, studies, particularly from northern countries, report series of carcinoma and multiple myeloma occurring after SSp [4-6, 8, 10, 12, 13]. In Africa, to our knowledge, there are no similar observations. Ssp usually occurs between the ages of 40 and 50, but it has been described that Ssp complicated by solid neoplasia occurs at a higher age (53.6 years) [4, 10, 12]. Zhang *et al*., even found a significant association between pSS and solid cancer in his cohort in 2012. Indeed, he found that SSp had an SIR of 2.12 (95% CI 1.27-3.31). The majority of these studies show a predominance of the female sex in the association of these 2 pathologies. This difference with our study can be explained by the small size of our study [4-6, 8, 10, 13, 14]. However, Brom et al in 2019 and Weng in 2011 found that the standardised incidence rate for SSp was higher in men than in women [5, 14].

There is a diagnostic delay in our study. The average diagnostic delay was about 13 years and the diagnostic interval about 9 years. This can be explained by the lack of access to resources to confirm the diagnosis due to the socio-economic context. Other factors to be noted are the low use of adequate diagnostic tools for the early detection of cancers.

Clinically and paraclinically, the manifestations of Sjögren's disease found in our study do not differ from those found in the literature. However, it was found that patients with SSp complicated by NHL had more lymphadenopathy, parotidomgaly, splenomegaly compared to patients with SSp associated with a solid tumour [10, 13].

Cancers were found to be metastatic in 60% of cases. The predominant metastasis was to the liver. This is explained by the delay diagnostic of tumours. The liver is the 2nd most common metastatic site for tumours after the lung [15].

SSp was associated with prostate (3 cases), ovarian (2 cases) and colon cancer (1 case). Numerous studies have published case series associating SSp with these cancers but these data were not statistically significant. Nevertheless, SSp has been found to be a risk factor for increased incidence of cancer of the thyroid, lip, tongue, oral cavity, stomach and breast [5, 8, 13, 14].

Hypotheses suggesting SSp as a paraneoplastic syndrome of solid tumours have been put forward, based on the assumption that this link is more important than that between SSp and NHL. However, this has not yet been confirmed and requires prospective work with large numbers of patients to answer [12].

The treatment of this association is not codified but relies on the empirical administration of treatment against SSp (MTX, HCQ, corticosteroid) and that of the tumour (chemotherapy, radiotherapy, surgery) [2].

The association of the two pathologies has a poor prognosis, especially since in our study the patients were at the metastatic stage. This is reflected in the unfavourable evolution and death of two patients.

CONCLUSION

In our study we find 5 observations of SSp and solid tumour. Our study reveals that the association occurs at an older age than that of isolated SSp. We note a delay in diagnosis leading to a poor prognosis marked by the discovery of metastases and death (in 2 patients). Close surveillance is necessary in all cases of SSp to allow early detection of cancer, particularly NHL, which is more frequent, but also solid tumours (thyroid, oropharynx, breast) which are statistically associated with it. The paraneoplastic hypothesis of SS is currently little studied despite data suggesting this

association. It would require further studies to confirm it.

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