



# Unusual association of two cases of acute myeloblastic leukaemia and possible Sjogren's syndrome and review of literature

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## Abstract

Sjögren's syndrome (SS) is frequently accompanied by hematologic complications, such as Hodgkin lymphoma. Here, we report on two unusual cases in which acute myeloid leukaemia (AML) and suspected SS occurred concomitantly. As has been observed for other malignancies, SS may be a paraneoplastic syndrome of AML.

**Keywords:** Sjögren's syndrome, acute leukaemia, dry eyes and mouth syndrome

## Introduction

Sjögren's syndrome (SS) is one of the most common autoimmune diseases, with a recently estimated prevalence in the general population of between 0.21% and 0.72% [1]. Sjogren's syndrome predominantly affects women, with a peak in incidence in the fifth decade of life [1]. The condition is characterized by lymphocytic infiltration of the exocrine glands and the production of autoantibodies. The clinical features are highly variable, although asthenia, dry mucous membranes, and painful muscles and joints predominate [2]. In 2002, the American-European Consensus Conference (AECC) published diagnostic criteria for SS [3]. Most recently, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed a new set of classification criteria. These include the presence of objective immunological abnormalities (such as a focal lymphocytic sialadenitis in labial salivary gland biopsy, with a focus score of  $\geq 1$  foci/4 mm<sup>2</sup>; 3 points), positivity for anti-sicca syndrome A (SSA) autoantibodies (3 points), and the presence of objective ocular signs (ocular staining score  $\geq 5$  or Schirmer's test  $\leq 5$  mm/min in at least one eye; 1 point) and oral signs (unstimulated whole saliva flow rate  $\leq 0.1$  mL/min; 1 point). Patients with a total score of 4 or more are classified as having primary SS with a sensitivity of 96% and specificity of 95% [4].

Various haematological abnormalities (such as anaemia, thrombocytopenia and leukopenia, in the presence or absence of auto-immune disease) are frequently reported in patients with

SS [5-7]. The risk of developing non-Hodgkin's lymphoma in SS is well documented, and associations with other haematological malignancies, although uncommon, have been described [8,9]. Here, we report on two cases of the concomitant occurrence of acute leukaemia (AL) and suspected SS, and review the literature on this topic.

## Case presentation

### Patient #1

A 72-year-old woman with a history of obstructive sleep apnoea syndrome and extrapyramidal syndrome (but no associated dementia) presented with poor general health status, myeloma and pancytopenia (white blood count:  $2.2 \times 10^3/\text{mm}^3$ ; haemoglobin: 10 g/dl; platelet count:  $147 \times 10^3/\text{mm}^3$ ). She was hospitalized in the intensive care department for pneumonia-related oxygen dependence. The myelogram revealed blast infiltration associated with acute myeloid leukaemia (AML) M4, according to the French-American-British (FAB) classification. Karyotyping revealed structural abnormalities and aneuploidy, including 5q deletion.

When interviewed, the patient reported dry eye syndrome, foreign body sensation in the eye, dry mouth syndrome, and asthenia and apathy for few weeks. A salivary gland biopsy revealed lymphocytic sialadenitis with non-specific atrophic damage (Chisholm-Mason grade 2). A comprehensive biological screen was positive for antinuclear antibodies (positive titre of

1:320, anti-SSA antibodies) and negative for anti-DNA antibodies. Lymphocytic immunophenotyping detected moderate B cell and CD8 T cell lymphopenia. The patient's poor general health status prevented us from performing confirmatory tests for SS. Although SS was strongly suspected, the ACR/EULAR criteria were not met, and so our final diagnosis was possible SS. Following the onset of septic shock with multi-organ failure, and in view of the severity of the underlying disease, we decided to discontinue resuscitation. The patient died soon after.

### Patient #2

A 65-year-old man with history of aortic native valve endocarditis, chronic obstructive pulmonary disease and chronic exogenous had been monitored for several years following the occurrence of aregenerative anaemia and macrocytosis, in association with leukopenia, neutropenia, and mild thrombocytopenia. The results of a bone marrow examination were suggestive of alcohol intoxication and vitamin B9 and B12 deficiency. The man was admitted to hospital for treatment of the pancytopenia. A second bone marrow examination revealed blast infiltration and prompted a diagnosis of secondary AML. The karyotype was normal.

A clinical examination revealed dry mouth syndrome, with no other functional signs. The patient has experienced severe asthenia for the previous two months. We were not able to perform functional tests that might have confirmed the dry mouth and eyes syndrome. A salivary gland biopsy revealed the presence of non-specific, inflammatory lesions around the salivary ducts. Laboratory tests were positive for antinuclear antibodies (positive titre of 1:1280, anti-SSA antibodies) and negative for anti-DNA antibodies. The plasma protein electrophoresis results were not suggestive of hypo- or hypergammaglobulinemia. The ACR/EULAR criteria were not met in this critically ill patient, and so our final diagnosis was possible SS. In view of the patient's poor general condition, comorbidities and the emergence of septic shock, we decided to discontinue chemotherapy. The patient died in the intensive care unit.

### Literature review

Although many studies have focused on the risk of neoplasia in SS [10-14], we found only four publications in which acute leukaemia was cited (Table 1) [15-18]. The first publication reported on a 59-year-old woman with primary SS diagnosed in 1963. She developed myelodysplastic syndrome soon afterwards. AML was diagnosed in 1974 (i.e., 11 years after diagnosis of the autoimmune disease) [15]. The second publication described a 53-year-old woman with dry eyes and mouth syndrome. The Schirmer test and sialography results were abnormal. A salivary gland biopsy revealed unorganized lymphocyte infiltration. Two years after symptom onset, the patient developed fatal AML [16]. The third report concerned a 55-year-old man who developed acute lymphoblastic leukaemia (ALL) seven years after the onset of seronegative primary SS [17]. The last case concerned a 48-year-old male who developed acute B-cell leukaemia five years after the diagnosis of primary SS [18].

### Discussion

We described two new cases of concomitant AL and possible SS. Four similar cases have been reported in the literature. Although our two patients presented with a dry eyes and mouth syndrome, a firm diagnosis of SS (according to the AECC or ACR/EULAR criteria) could not be made. SS cannot be diagnosed unless it is specifically screened for, and the documentation of dry eyes and mouth syndrome is often difficult in critically ill patients. A retrospective study of Swedish patients with "non-AECC" sicca syndrome did not observe an increased risk of cancer (standardized incidence ratio [95% confidence interval]: 0.77 [0.41-1.32]). Interestingly, neither acute leukaemia nor lymphoma was diagnosed [11].

Patients with SS have a high prevalence of lymphoid haematological malignancies, such as chronic lymphocytic leukaemia, large granular lymphocytic (LGL) leukaemia and, above all, lymphoma [19-21]. In patients with LGL leukaemia, SS was the most frequently associated autoimmune disease (ahead of rheumatoid arthritis) [20]. Identical phenotypes of circulating lymphocytes and lymphocytes in the salivary glands may

Table 1. Characteristics of the present cases and those described in the literature.

Patient	Sex	Reference	Age* (years)	Type of SS	Time interval**	Type of leukaemia	Outcome
1	F	Patient #1	72	Possible SS	concomitant	AML	Death
2	M	Patient #2	65	Possible SS	concomitant	AML	Death
3	F	[15]	59	AECC, primary	11 years	AML	?
4	F	[16]	53	AECC, primary	2 years	AML	Death
5	M	[17]	55	AECC, primary	7 years	ALL	?
6	M	[18]	43	AECC, primary	5 years	ALL	?

F: female; M: male; SS: Sjögren's syndrome; AECC: American-European Consensus Conference; AML: acute myeloid leukaemia; ALL: acute lymphoid leukaemia.

\*Age at diagnosis of SS. \*\* Time interval between the diagnosis of SS and the emergence of acute leukaemia.

suggest LGL infiltration of the salivary glands [21]. Although an association between SS and myeloid haematological malignancy is rare, cases of myelodysplastic syndrome, chronic myeloid leukaemia and chronic myelomonocytic leukaemia have already been described [22,23].

In most cases, SS was diagnosed several years before leukaemia. The use of immunosuppressant and immunomodulatory drugs in SS with visceral damage or disabling dry eyes and mouth syndrome might influence the occurrence of haematological malignancies [24]. However, Lazarus et al. did not find any significant differences in the use of drugs like hydroxychloroquine, prednisone, azathioprine and methotrexate (the main compounds used to treat severe forms of SS) when comparing primary SS patients with versus without cancer [18].

SS lies on the boundary between autoimmunity and lymphoproliferation. In this context, development of ALL might be related to the emergence of an immortalized clone. The mechanisms underlying the formation of AML are more difficult to understand. Furthermore, the very low incidence of this association makes it difficult to perform fundamental research. Well-conducted epidemiological studies of the association between SS and AL are now warranted. However, the simultaneous occurrence of these two diseases is suggestive of a causal relationship. Two arguments notably indicate that the possible SS observed in our two patients can be viewed as a paraneoplastic syndrome: (i) the acute onset and rapid progression of SS, and (ii) the short time interval between the onset of the dry eyes and mouth syndrome and the occurrence of acute leukaemia. Some observations suggested the possible paraneoplastic character of SS [25,26].

## Conclusion

We described two uncommon cases of concomitant possible SS (dry eyes and mouth syndrome, and positivity for anti-SS-A/Ro antibodies) and AML. Our patients' critical health status and subsequent death prevented us from evaluating all the ACR/EULAR criteria. The possible SS in our patients may have been a paraneoplastic syndrome.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

Authors' contributions	CB	CG	MC	AP	JPM
Research concept and design	--	--	--	--	--
Collection and/or assembly of data	✓	--	✓	✓	--
Data analysis and interpretation	--	--	--	--	--
Writing the article	✓	✓	--	--	✓
Critical revision of the article	✓	✓	✓	--	✓
Final approval of article	✓	✓	✓	✓	✓
Statistical analysis	--	--	--	--	--

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