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REVIEW

Sjögren protein-losing enteropathy: a systematic review

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Background: Sjögren protein-losing enteropathy (SPLE) is a rare manifestation of Sjögren syndrome (SS). This study aimed to identify the characteristics of patients with SPLE.

Methods: A systematic review was performed with 22 patients who met the eligibility criteria and were critically appraised. Technetium-99m (99mTc) albumin scintigraphy or a faecal alpha-1 antitrypsin (A1AT) clearance test was ultimately used to identify SPLE.

Results: Patients' clinical features at the time of SPLE diagnosis were 51.8 ± 16.3 years, and the female-to-male ratio was 8.1:1. In most cases (86%), the SS diagnosis was retained as part of the aetiological investigation of protein-losing enteropathy (PLE). Serologically, anti-Ro was present in all cases and anti-La in 49%.

Conclusion: In this review, 15 cases underwent 99mTC human serum albumin (HSA). Protein leakage was positive in all the above cases. A 24-hour stool specimen showed a positive faecal A1AT clearance test. This is the first systematic review of SPLE associated with SS.

Keywords: Sjögren syndrome, protein-losing enteropathy

Introduction

SS is a systemic autoimmune disorder that causes lymphocytic infiltration of exocrine glands, with a higher frequency in females.[1] The reported prevalence of people with SS ranges from 113 306 to 4.5 million, with an incidence of 0.03–0.77%.[1] There are two types, primary Sjögren syndrome (pSS) and secondary Sjögren syndrome (sSS), where sSS refers to the presence of other connective tissue diseases while pSS is encountered alone.[2] The condition is characterised by exocrinopathy, which can cause a dry mouth and eyes and weariness. PSS can be associated with various organs, including joints, kidneys, thyroid, neurological system, lungs, and gastrointestinal tract.[3]

Gastrointestinal involvement has been described in patients with SS. The mouth and oral cavity are the most heavily affected organs in SS, resulting in symptoms like xerostomia, tooth alterations, and dysgeusia. Other intestinal organs may also be affected, leading to gastroesophageal reflux disease, atrophic gastritis, and pancreatitis. One uncommon complication of autoimmune diseases, particularly SS, is PLE.[4,5]

This study aimed to analyse the clinical, therapeutic, and outcome characteristics of patients with SS and PLE and delineate the potential mechanisms and pathways connecting the gut to SS-targeted organ pathology.

Methods

A systematic literature review was done to identify articles that report PLE in patients with SS. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed for reporting systematic reviews and meta-analyses.[6]

Database search strategies

Systematic screening was conducted using PubMed/MEDLINE, LILACS, SciELO, Web of Science, and Cochrane/OVID, dating from 1980 to 2024. Sjögren syndrome and protein-losing enteropathy were the keywords.

Medical subject headings (MeSH) included "Adult", "Sjogren's Syndrome", "Sjogrens", "Sjögren", "Sjögren's", "Sjogren", "Gougerot", "Gougerot-Sjogren", "Gougerot-Sjögren", "Primitive Gougerot-Sjögren", "Gougerot-Sjögren", "Gougerot Houwers-Sjögren", "Protein-losing enteropathy", "Protein-Losing Enteropathy", and "Lymphangiectasis, Intestinal". MeSH words were combined with keywords via Boolean operators (OR, AND, NOT) and wildcards. The search was not limited by year, language, or place of origin; however, filters for species (humans) and ages (adults) were used. Manual searches were also performed as a supplement.

We also looked for further studies in the listed studies' bibliographies. Two reviewers (RBS and SM) independently reviewed the identified articles. They conducted a risk of bias assessment according to the Cochrane Collaboration's tool for eligible trials, and disagreement was discussed with a third author (ZB).[7] We excluded animal and experimental studies and paediatric observation. After study selection, 19 articles related to this review were included (Table III).

Inclusion and exclusion criteria and the screening process

Randomised controlled trials, retrospective studies, case reports, and prospective studies that reported SS and PLE were included in this review. There were no restrictions on patient sex or race.

Articles eligible to be included in this review were required to meet the following criteria:

1. Papers describing patients with SS diagnosed based on the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) criteria for the classification of pSS.[8]
2. Papers studying PLE attributable to SS.
3. PLE diagnosis based on objective clinical and biological signs confirmed by detecting A1AT in a stool sample or using 99mTc albumin scintigraphy (99mTc-HSA).[9]
4. Human subjects involved with SS and diagnosed based on clinical, laboratory, and histological examinations.

The exclusion criteria were:

1. Comorbidities that could be associated with PLE.
2. Duplicate papers or papers referring to the same patient population.
3. Articles where the full text was not available.

Three authors blindly reviewed all paper titles and abstracts. Those that did not meet the inclusion criteria were removed. Any discrepancies were resolved through consensus-building discussions, during which the abstracts were evaluated.

Data collection process

We extracted data using Excel in a systematic coding scheme to record the nature of the study, population size, age and sex distribution, first diagnosis, clinical symptoms at first diagnosis, mean age at each diagnosis, means of diagnosis for each condition, biological findings, means of treatment, and response to treatment.

Compliance with ethical guidelines

The article is based on previous studies or case reports. Consequently, there were no ethical concerns regarding the current study, and the research protocol did not require authorisation from an ethics committee.

Results

Clinical features

This systematic review identified 22 cases of reported SPLE. These were mainly case reports described in the literature. The Asian ethnicity was predominant. Only three cases were non-Asiatic.[5,10,11] The mean age at presentation was 51.8 ± 16.3 years (range 20–84). There were 18 women and four men. The distribution of cases according to age is presented in Table I.

Table I: Distribution of Sjögren protein-losing enteropathy cases according to age

Age (years)	*n* (%)
< 40	5 (22.7)
40–60	11 (50)
≥ 60	6 (27.2)

In most cases (86%), the SS diagnosis was retained as part of the aetiological investigation of PLE. Only three patients had been diagnosed with SS before PLE. PSS was observed in most cases (19/22, 86%), with one patient having concomitant lupus, another having rheumatoid arthritis, and the last having a mixed connective tissue disease.[12-14] Serologically, anti-Ro was present in all cases and anti-La in 49%.

Regarding clinical manifestations of protein loss, the majority presented with lower limb oedema (17/22), pleural effusion (19/22), ascites (5/22), pericardial effusion (1/22), facial oedema (5/22), anasarca (5/22), and diarrhoea (3/22).

The most frequent biological abnormality was hypoalbuminaemia. The albumin concentration before therapy was 0.5–3.4 g/dl, increasing to 2.8–4.3 g/dl post-therapy (Table II). No significant liver disease was reported. The 24-hour urine protein was less than 0.5 g in all cases.

Table II: Range of serum albumin in Sjögren protein-losing enteropathy

Albumin (g/dl)	*n*
< 3	18
3–3.5	3
> 3.5	0

In this review, 15 cases underwent 99mTc HSA. Protein leakage was positive in all these cases. The most common protein leakage site was the small intestine in 9/15 cases (60%), and the stomach in seven cases. The least common site was the colon (2/15, 13%). A 24-hour stool specimen is preferred over a spot sample. Eight patients underwent this test, and all showed a positive faecal A1AT clearance test.

Intestinal biopsy was performed in 21/22 cases. According to the literature study, characteristic findings in biopsy specimens from the affected alimentary tract wall include inflammatory cell infiltration, oedematous interstitial tissue, atrophied villi, and lymphangiectasis. Three case reports involved immunohistochemical labelling; two of them demonstrated perivascular deposition of Immunoglobulin G and C3, but the other did not.[15]

All patients received glucocorticoids, between 30 and 70 mg per day of prednisone, and 7/22 patients received a pulse of methylprednisolone.[13,16-21] Only 3/22 patients received albumin infusions, with little or questionable efficacy.[12,13,18] The use of immunosuppressants, such as cyclophosphamide, was provided in 4/22, mizoribine in three patients, and mycophenolate mofetil in one patient, but rituximab, intravenous immunoglobulin, and cyclosporine were given to only one patient.[11,13,15,18-20,22] Unsurprisingly, all patients showed signs of improvement with therapy. The onset of improvement ranged from three weeks to 36 months, with an average of three months. Table III summarises the main features of all reported cases of SPLE.

Discussion

In this review, only 22 cases of SPLE were collected. The limited number is explained by the relative rarity of this manifestation in SS. A 2–3% prevalence of PLE is reported among Asian

Table III: The main features of all reported cases of SPLE

First author	Year	Age	Sex	Nationality	Alb (g/dl)	SSA	SSB	ANA	Complications	Steroid	Other therapy	Outcome	Reference
Sugiyama	1991	47	F	Japanese	1.6	Pos	Neg	64	Chronic thyroiditis	PSL 60 mg (p.o.)		Improved	24
Mok	1997	54	F	-	1.4	ND	ND	ND	-	PSL 60 mg (p.o.)	CPA 100 mg	Improved	22
Hsieh (case 1)	2002	37	F	Taiwanese	1.4	Pos	ND	320	n.p.	mPSL 750 mg × 3 d 2-course (IV) + PSL 30 mg (p.o.)	HCQ 200 mg	Improved	16
Hsieh (case 2)	2002	50	F	Taiwanese	1.1	Pos	ND	640	n.p.	mPSL 750 mg × 3 d 3-course (IV) + PSL 30 mg (p.o.)	HCQ 200 mg	Improved	16
Choi	2004	50	F	Korean	1.4	ND	ND	ND	ND	PSL 60 mg (p.o.)		Improved	
Ushiyama	2004	61	F	Japanese	1.8	Pos	Neg	320	Chronic thyroiditis	PSL 40 mg (IV)		Improved	25
Nagashima	2009	41	M	Japanese	1.3	Pos	Pos	1 280	n.p.	PSL 70 mg (IV) + mPSL		Improved	17
Nasu	2011	59	F	Japanese	2.8	Pos	Neg	ND	RA, chronic thyroiditis	PSL 50 mg (p.o.) + mPSL 1 g × 3 d 2-course (IV)	CPA pulse + MZR 150 mg	Improved	13
Uraoka	2012	42	F	Japanese	1.5	Pos	ND	ND	n.p.	mPSL 1 000 mg × 3 d (IV) + PSL 20 mg (p.o.)	CPA pulse + rituximab	Improved	18
Kakigao	2012	58	F	Japanese	1.5	Pos	Neg	ND	MCTD, hypothyroidism	PSL 45 mg (p.o.)		Improved	14
Chen	2013	69	F	Chinese	ND	Pos	Pos	ND	ND	PSL (p.o.) + mPSL (IV)		Improved	21
Yamashita	2014	51	F	Japanese	1.5	Pos	Pos	2 560	Interstitial pneumonia	PSL 60 mg (p.o.)		Improved	26
Liao	2015	30	F	Taiwanese	1.8	Pos	ND	5 120	n.p.	PSL 30 mg (p.o.)	HCQ 400 mg	Improved	27
Gupta	2015	58	F	American Caucasian	2.6	Pos	Pos	1 280	Type 1 RTA	PSL 60 mg (p.o.)	CPA 800 mg/mo		11
Izumi	2018	64	F	Japanese	3.0	Pos	Neg	Neg	n.p.	PSL 50 mg (p.o.) + mPSL 500 mg × 3 d (IV)	Mizoribine 200 mg	Improved	19
Eguchi	2018	20	F	Japanese	0.9	Pos	Pos	1 280	LES	Prednisone 50 mg, IV albumin		Improved	12
Watanabe	2018	88	M	Japanese	2.8	Pos	Pos	40	n.p.	PSL 30 mg (p.o.) + mPSL 1 000 mg (IV)	IVIG 20 g + theophylline	Improved	20
Li	2019	71	M	Chinese	2.7	Pos	Pos			Methylprednisolone 40 mg IV once a week and p.o.		Improved	28
Nakamura	2019	46	F	Japanese	1.2	Pos	Pos	1 000		Prednisolone 40 mg	Mizoribine 100 mg CYA	Improved	23
Akaishi	2020	30	M	Japanese	3.4	Pos	Neg			Prednisolone 40 mg, MMF		Improved	15
de Carvalho	2021	34	F	Brazilian	3.4	Pos	Neg	160		Betamethasone dipropionate IM, HCQ, MTX, AZA		Improved	5
Zucman-Rossi	2023	84	F	French	0.5	Pos	Pos	1 280		Corticoide 0.5 mg/kg Plaquenil 400 mg		Improved	10

Alb – albumin, ANA – antinuclear antibody, AZA – azathioprine, CPA – cyclophosphamide, CYA – cyclosporine A, d – day/s, F – female, HCQ – hydroxychloroquine, IV – intravenous, IVIG – intravenous immunoglobulin, M – male, MCTD – mixed connective tissue disease, MMF – mycophenolate mofetil, mPSL – methylprednisolone, MTX – methotrexate, MZR – mizoribine, ND – not determined, Neg – negative, n.p. – not performed, p.o. – per os (by mouth), Pos – positive, PSL – prednisolone, RA – rheumatoid arthritis, RTA – renal tubular acidosis, SLE – systemic lupus erythematosus, SSA – anti-SS-A antibody, SSB – anti-SS-B antibody

patients with systemic lupus erythematosus (SLE).[29] In a study of 24 patients with ileal Crohn's disease in clinical remission, all exhibited laboratory evidence of PLE (but none had clinical symptoms), implying that the prevalence of PLE may be greatly underestimated.[25]

The mean age at presentation in our study was 51.8 ± 16.3 years. The mean age in the lupus-associated PLE group was 34.3 ± 14.2 years.[30] This result is due to the age of discovery of SS, generally between 50 and 60 years (i.e. the age of perimenopausal women).[3] The most common clinical presentation was peripheral oedema (77%) and pleural effusion (86%). This study showed that most Sjögren patients do not have diarrhoea. There were no reported cases of bloody diarrhoea.

Infectious causes should be excluded in SPLE. The presence of severe oedema and marked hypoalbuminaemia without significant proteinuria should raise the suspicion of PLE. To establish a PLE diagnosis, other causes of hypoalbuminaemia must be excluded, particularly fluid overload (e.g. congestive heart failure), reduced protein synthesis (e.g. chronic liver disease), undernutrition, and other causes of serum protein decrease (such as nephrotic syndrome).

Because protein loss in PLE occurs regardless of molecular weight, these patients commonly have low albumin and globulin levels in their serum.[31] If there are isolated low serum albumin and normal serum globulins, alternative causes should be considered, but in SS, the serum globulin can be in the normal range or increased. The increase in gamma globulin is a particularity in patients with SS, so that the gamma globulin can be in the normal range in SS despite the presence of PLE.[10,15,20]

A1AT intestinal clearance is the primary and most commonly used test to identify PLE. This protein has a high molecular weight, undergoes low degradation in the gut, and is excreted intact. Its clearance is calculated by 24-hour stool collection and measuring A1AT in serum and stool.[9] These tests may also be used to check treatment efficacy. However, it is crucial to highlight the following recommendation: another test, Chromium-51-labeled albumin clearance (considered the gold standard), and 99mTc-labelled serum albumin scintigraphy can also be conducted in case of high clinical suspicion of PLE with a negative A1AT clearance test.

Nuclear medicine studies have been used in 15 cases in this review to characterise the leakage site, but they require special radiolabelled proteins and expertise. These tests have excellent sensitivity but are exceedingly laborious, expensive, and not frequently available, so they are not routinely used. In some cases of focal intestinal lymphangiectasia, lymphangiography or dynamic contrast-enhanced magnetic resonance lymphangiography can reveal the location of lymphatic leakage, which can help guide interventional therapy.

When PLE is diagnosed, it should be evaluated, and further testing is required to uncover the underlying cause and guide treatment. PLE is related to various disorders that frequently impact multiple organ systems and can be classified into digestive and non-digestive causes.[9] Gastrointestinal sources are further classified as erosive and non-erosive conditions of the gut that result in protein loss across the intestine's mucosal membrane.[32] This evaluation should involve a comprehensive history, physical examination, and typical evaluations of other reasons for hypoalbuminaemia, as mentioned. Endoscopy and biopsy should be performed to detect anatomical abnormalities, blockage, mucosal inflammation, ulceration, dilated lacteals, lymphangiectasia, and neoplasms. An intestinal biopsy was conducted in all patients, revealing mild inflammatory infiltrates and lamina propria oedema.

Interestingly, the cases herein published all had anti-Ro positivity. Moreover, a previous study in SLE patients demonstrated that this antibody is a risk factor for PLE.[30] This fact might suggest that anti-Ro may play a role in PLE pathophysiologic evolution. It is not unusual that active PLE patients have normal levels of faecal A1AT, which does not rule out the diagnosis. Several studies reported a false negativity of this stool marker in PLE.[9]

PLE is a systemic spectrum of pSS extending out of the EULAR Sjögren Syndrome Disease Activity Index (ESSDAI), either by features corresponding to organs/systems not currently included (digestive, inflammatory ocular, urological, ear, nose, and throat) or by features not included in the corresponding ESSDAI organ-specific domain (cutaneous, peripheral nerve, etc.). The authors propose incorporating gastrointestinal signs in the ESSDAI, citing that the presence of PLE in SS indicates a more severe condition. Future studies should assess the addition of gastrointestinal aspects to the ESSDAI score.

Glucocorticoids at high doses are necessary for treating PLE in SS. Parenteral administration of this medicine appears to have superior results, possibly due to intestinal malabsorption that may be present, making corticosteroid absorption rather difficult. Corticosteroids were highly effective, and the prognosis for a combination of steroids with immunosuppressive therapy was quite good. Only one case report illustrated that treatment is purely anecdotal because of the lack of controlled trials. The use of immunosuppressants is reserved in the absence of amelioration with steroids. Information on the relapse rate from historical cases was scarce because most reports only concentrated on the short-term treatment response.

Supplemental therapy, such as serum albumin infusions and diuretics, should be administered simultaneously. In addition, octreotide could reduce intestinal microvascular blood flow, decrease local lymph formation, and ameliorate lymphatic dilation.

The interaction between the failure of the intestinal mucosa in PLE and the malfunction of the moistening exocrine glands in SS is a topic of interest. Both entities share multiple aspects. Nutrition and nutrients might impact gut tight junction integrity, and SS is affected by nutrition.[33] The microbiome/dysbiome ratio is affected in SS.[33] Finally, chronic stress or acutely stressful events, like the death of loved ones, affect both SS and multiple

PLE-associated entities.[34,35] More research is needed to uncover the secrets of the SS-PLE axis.

Conclusion

This systematic review analysed all documented instances of the uncommon correlation between SS and PLE. After testing out renal, hepatic, and heart problems, the treating physician should be directed to suspect PLE if oedema and hypoalbuminaemia are present in patients with SS. Corticosteroid medication should be started promptly to prevent future worsening, complications, and morbidity. It is imperative to be more aware of the gastrointestinal symptoms of SS and to do an extensive investigation to rule out PLE and its causes.

Conflict of interest

The authors declare no conflict of interest.

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