



HAL
open science

TAFRO syndrome: A severe manifestation of Sjogren's syndrome? A systematic review

Lucile Grange, Emilie Chalayer, David Boutboul, Stéphane Paul, Lionel Galicier,
Baptiste Gramont, Martin Killian

► **To cite this version:**

Lucile Grange, Emilie Chalayer, David Boutboul, Stéphane Paul, Lionel Galicier, et al.. TAFRO syndrome: A severe manifestation of Sjogren's syndrome? A systematic review. *Autoimmunity Reviews*, 2022, 21, <10.1016/j.autrev.2022.103137>. <hal-04872739>

HAL Id: hal-04872739

<https://hal.science/hal-04872739v1>

Submitted on 8 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization



TAFRO syndrome: A severe manifestation of Sjogren's syndrome? A systematic review

Lucile Grange^a, Emilie Chalayer^{b,c}, David Boutboul^{d,e,f}, Stéphane Paul^{g,h,i}, Lionel Galicier^{d,e}, Baptiste Gramont^{a,h}, Martin Killian^{a,h,i,*}

^a Department of Internal Medicine, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, France

^b Department of Hematology and Cell Therapy, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, France

^c Inserm U1059-SAINBIOSE, dysfonction vasculaire et hémostasie, Université de Lyon, Saint-Etienne, France

^d Clinical Immunology Department, Hôpital Saint Louis, Université Paris Cité, Paris, France

^e National Reference Center for Castleman disease, Hôpital Saint Louis, Université Paris Cité, Paris, France

^f U976 HIPI, INSIGHT Team, Hôpital Saint Louis, Université Paris Cité, Paris, France

^g Department of Immunology, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, France

^h CIRI – Centre International de Recherche en Infectiologie, Team GIMAP, Université Jean Monnet, Université Claude Bernard Lyon 1, Inserm, U1111, CNRS, UMR530, F42023 Saint-Etienne, France

ⁱ CIC 1408 Inserm, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, France

ARTICLE INFO

Keywords:

TAFRO syndrome
Castleman disease
Sjogren's syndrome
Review
Anasarca
Thrombocytopenia

ABSTRACT

Background: Sjögren's syndrome (SjS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands associated with sicca syndrome. TAFRO syndrome is a systemic inflammatory disease of unknown cause, characterized by Thrombocytopenia, Anasarca, Fever, Reticulin fibrosis, Renal dysfunction and Organomegaly, first reported in 2010 in Japanese patients. Despite their rarity, both conditions have been concurrently reported in several patients during the recent years, hence questioning the existence of shared or related features.

Methods: A systematic review of the literature regarding SjS associated with TAFRO syndrome (SjS-TAFRO) was performed. The 2019 updated Masaki diagnostic criteria were used for TAFRO syndrome and SjS was considered when the diagnosis was mentioned by the authors, necessarily with either anti-Sjogren's Syndrome A (SSA) ± anti-Sjogren's Syndrome B (SSB) antibodies and/or histological evidence of focal lymphocytic sialadenitis.

Results: Ten cases of SjS-TAFRO have been reported in the literature to date. Compared to SjS patients without TAFRO syndrome, these 10 SjS-TAFRO had a lower female predominance (2.3:1 vs 9:1 women to man *ratio*) and a higher frequency of anti-SSA antibodies (90% vs 70%). All fulfilled the three major Masaki criteria *i.e.*, anasarca, thrombocytopenia, and systemic inflammation. Seven of them (70%) had megakaryocyte hyperplasia or reticulin fibrosis in the bone marrow. Lymph node biopsy was performed in 8 out of 10 cases (80%) and results were consistent with Castleman disease in 6 (75%). Eight of them had developed renal failure (80%) within six months. Nine of them (90%) had organomegaly, with hepatosplenomegaly in 8 cases and splenomegaly alone in 1.

Conclusion: This review brings new insights regarding TAFRO syndrome and suggests it could be a severe manifestation of SjS. The identification of shared abnormal signaling pathways could help in the therapeutic management of both diseases, which face an unmet therapeutic need.

Abbreviations: SjS, Sjögren's syndrome; iMCD, idiopathic multicentric Castleman disease; IQR, interquartile; IL, interleukin; VEGF, vascular endothelial growth factor; OSS, Ocular staining score; PSL, prednisolone; AZA, azathioprine; CyA, cyclosporine A; CYP, cyclophosphamide; FMD, furosemide; mTOR, mammalian Target Of Rapamycin; ALP, alkaline phosphatase; WBC, white blood cells; CRP, C-reactive protein.

* Corresponding author at: Service de Médecine Interne, Batiment C 5ème étage, Hôpital Nord, Centre Hospitalier Universitaire de Saint-Etienne, 42055 Saint-Etienne Cedex 02, France.

E-mail address: martin.killian@chu-st-etienne.fr (M. Killian).

<https://doi.org/10.1016/j.autrev.2022.103137>

Received 8 June 2022; Accepted 4 July 2022

Available online 6 July 2022

1568-9972/© 2022 Elsevier B.V. All rights reserved.

1. Introduction

Sjögren's syndrome (SjS) is the second most common systemic autoimmune disease after rheumatoid arthritis, affecting 0.01–0.3% of the adult population worldwide [1–3]. It has a peak age of onset between 40 and 60 years, and a 9:1 female to male sex ratio [4]. SjS is characterized by lymphocytic infiltration of the salivary and lacrimal glands, associated with xerostomia and xerophthalmia. Between 0.5% and 40% of the patients develop systemic complications, such as renal, pulmonary or neurological manifestations [5–8]. SjS's most severe complication is lymphoma which develops in 5% of the cases [9–11].

TAFRO syndrome is a systemic inflammatory disease of unknown cause, characterized by Thrombocytopenia, Anasarca (oedema, pleural effusion, and ascites), Fever, Reticulin Fibrosis, Renal insufficiency and Organomegaly (hepatosplenomegaly and lymphadenopathy) [12]. It was first reported by Takai et al., in 2010 in Japanese patients [13], and has now been described in all ethnicities [14,15]. TAFRO syndrome is mainly regarded as a severe subtype of idiopathic (*i.e.*, Human Herpes Virus-8 [HHV-8] negative) multicentric Castleman disease (iMCD), referred to as iMCD-TAFRO (whereas iMCD without TAFRO syndrome is called iMCD-not otherwise specified [iMCD-NOS]) according to the first-ever consensus diagnostic criteria for iMCD proposed by the Castleman Disease Collaborative Network (CDCN) in 2017 [16]. Others think it is still unclear if TAFRO syndrome is indeed a subtype of iMCD, a clinical entity overlapping with iMCD, or a unique disease, possibly driven by autoimmunity, which can be coincidentally accompanied by an iMCD-like lymph node histopathology [12,17]. Moreover, during the last decade, several cases of TAFRO syndrome have been described worldwide in patients without biopsy-proven Castleman disease, because severe thrombocytopenia and/or small volume lymphadenopathy can make a lymph node biopsy difficult or contraindicated [18]. In line with this, the 2015 and 2019 diagnostic criteria for TAFRO syndrome proposed by the Japanese TAFRO Syndrome Research Team (*i.e.*, the Masaki criteria) have never included histological evidence of Castleman disease as a mandatory criterion [12,19], considering that iMCD-TAFRO and TAFRO-without-proven-iMCD could be the same clinical entity [12,20]. In fact, TAFRO syndrome has frequently been associated with other comorbidities than iMCD, including infectious diseases, malignancies or autoimmune diseases, as reflected by the identification of a “TAFRO syndrome, not iMCD-TAFRO” class in the latest international definition of iMCD-TAFRO by Nishimura et al. [21]. An important point, since the very first proposed diagnostic criteria for TAFRO syndrome [12], has been the exclusion of multiple diseases which could partly or totally mimic TAFRO syndrome, such as systemic lupus erythematosus (SLE) [22], or Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin abnormalities (POEMS) syndrome. Regarding SjS, the justification for its specific addition to the list of diseases to be excluded during differential diagnosis in the 2019 updated Masaki criteria [19], is a matter of debate. The authors justify such an addition as “a considerable number of patients with SjS were registered in their retrospective database”, however the TAFRO-mimicking potential of SjS is far from obvious: anasarca, non-tubular renal involvement, or cytopenia secondary to myelofibrosis are particularly rare in SjS [8,23]. Hence, another possible hypothesis could be that TAFRO syndrome and SjS are linked.

The purpose of the present study was to carry out a comprehensive literature review to identify cases of SjS associated with TAFRO syndrome (SjS-TAFRO) and summarize the shared pathophysiological mechanisms between the two syndromes.

2. Methods

2.1. Study selection

We have included case reports describing concomitant diagnoses of SjS and TAFRO syndrome, *i.e.*, SjS-TAFRO, regardless of the timing

between both diagnoses. The 2019 updated Masaki criteria were used for TAFRO syndrome [19], *i.e.*, 1) three required major criteria: anasarca (including pleural effusion, ascites and general oedema); thrombocytopenia (platelet count $\leq 100,000/\mu\text{L}$ without myelosuppressive treatment); systemic inflammation (fever of unknown etiology above 37.5°C and/or serum C-reactive protein concentration $\geq 2\text{ mg/dL}$) and 2) two minor criteria among: Castleman disease-like features on lymph node biopsy; reticulin myelofibrosis and/or increased number of megakaryocytes in bone marrow; mild organomegaly (including hepatomegaly, splenomegaly and lymphadenopathy); progressive renal insufficiency. Fulfilment of the 2021 international definition of iMCD-TAFRO by Nishimura et al., was also looked upon [21]. SjS was considered when the diagnosis was mentioned by the authors along with sicca syndrome (with or without objective examination) and necessarily with either the presence of anti-Sjogren's Syndrome A (SSA) \pm Sjogren's Syndrome B (SSB) antibodies and/or histological evidence of focal lymphocytic sialadenitis. All diagnoses were reviewed by two authors (LG, MK) prior to any inclusion. All types of original studies, including clinical trials, observational studies, case series, case reports, and letters to the editor were studied. Narrative and systematic literature reviews, and meta-analyses were excluded.

2.2. Data sources and searches

The computer-assisted search was carried out in the following electronic databases: MEDLINE and Google Scholar without time restriction. The following search strategy equation was used to identify relevant articles in PubMed: “(‘Sjögren’ OR ‘Sjogren’ OR ‘Sjögren's syndrome’ OR ‘Sjogren's syndrome’ [MeSH Term]) AND (‘TAFRO’ OR ‘TAFRO Syndrome’ OR ‘Castleman’ OR (‘Castleman disease’ [MeSH Term]) OR ‘anasarca’ OR (‘oedema’ [MeSH Term]))”. As TAFRO syndrome has only been defined as such in 2010 but is thought to be (at least partly) related to iMCD, we have included MCD terms in the research. The reference lists of all selected articles have also been manually checked to identify additional case reports of interest. Two review authors (LG and MK) screened all the titles and abstracts which were identified *via* the pre-defined search strategy. When an abstract was identified as potentially eligible for inclusion by at least one of the two review authors, the full text-articles were reviewed before considering any inclusion.

2.3. Data extraction and management

Two authors (LG and MK) have independently extracted the following data: demographics, TAFRO syndrome and SjS-related features, laboratory parameters, treatments and outcomes.

2.4. Data analysis

Data were presented either as median with interquartiles (IQR) for quantitative variables or as absolute numbers with percentages for qualitative variables.

3. Results

3.1. Study selection

The search procedure identified 172 eligible references. One hundred and fifty-six were excluded after review of their titles and abstracts (Fig. 1). After assessment of the full texts, 6 additional references were excluded: five because TAFRO syndrome criteria (notably thrombocytopenia) were not fulfilled and one because both diagnoses (TAFRO syndrome and SjS) were excluded. Finally, 10 case reports were included in the systematic review.

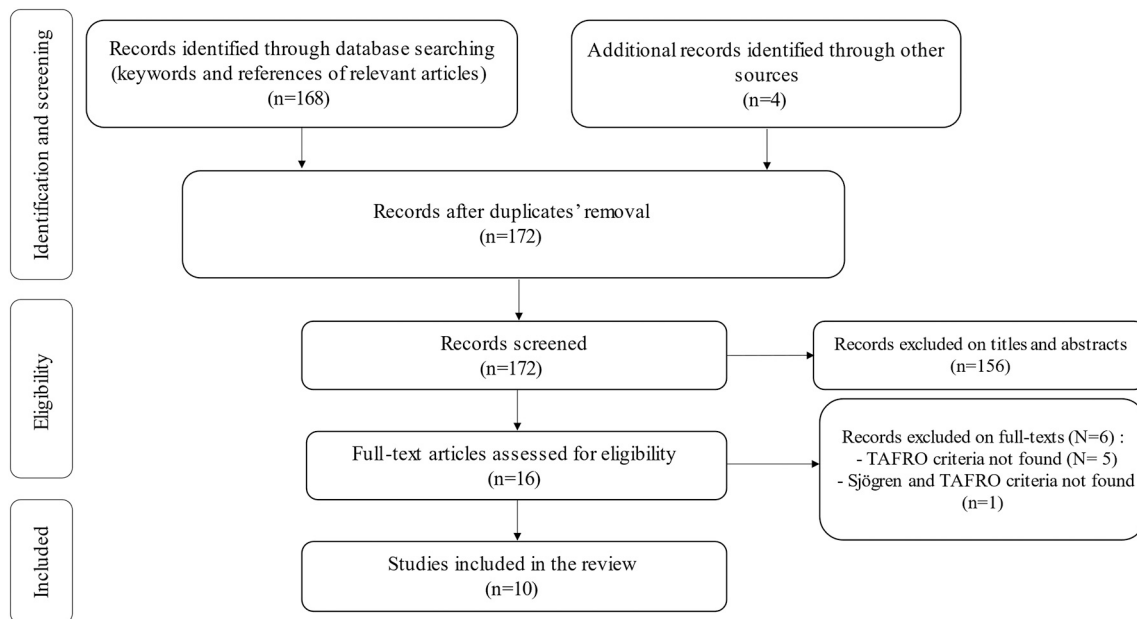


Fig. 1. Flow chart of the systematic review.

3.2. Characteristics of the patients

Ten cases of SJS-TAFRO had been reported in the literature to date [18,24–31]. The main features of all 10 cases were summarized in Table 1 and their biological results at admission in Table 2. Seven patients were females, and 3 patients were males, with a female/male sex ratio of 2.3:1. The median age was 48 years old [IQR 33–51.8]. In all the described cases, both diagnoses, TAFRO syndrome and SJS were clearly established. The diagnoses were made concomitantly (within a 3 month timeframe) in 8 cases (80%) [18,26–32]. In the two other cases, the diagnosis of SJS was made before (1 and 18 years earlier) the diagnosis of TAFRO syndrome [24,25].

All patients fulfilled the 2019 updated Masaki criteria as well as the international definition by Nishimura et al., for TAFRO syndrome not iMCD-TAFRO [19,21]. Lymph node biopsy was performed in 8 out of 10 cases (80%). In one case the biopsy could not be performed due to severe thrombocytopenia and in the other case, there was no lymphadenopathy. Results were consistent with Castleman disease in 6 (75%), and not conclusive in 2 (25%). Among the 6 patients with lymph node biopsy consistent with Castleman disease, three were compatible with the mixed subtype [25,27,28], two with the plasmocytic subtype [26,31] and one with the hyaline vascular subtype [30].

Seven out of ten patients (70%) had an increased number of megakaryocytes or reticulin fibrosis in the bone marrow (regarding the 3 remaining cases: the bone marrow biopsy was normal for two and missing for the other). Nine cases (90%) had organomegaly: hepatosplenomegaly in 8 cases and splenomegaly only in one case. Eight cases experienced renal dysfunction (80%) (elevated creatinine and/or proteinuria) during their follow-up (regarding the 2 remaining cases: kidney function remained normal for one patient and data was missing for the other). All developed renal failures within 6 months (at diagnosis for 5 of them). One patient (10%) was admitted in intensive care unit and temporally required dialysis during his first flare [31]. The median of the highest reported serum creatinine level during follow-up for all patients was 97.7 [IQR 79.2–141.0] $\mu\text{mol/L}$. Among these 8 patients, 5 had both elevated creatinine and proteinuria [18,26,27,30,31], 2 patients had proteinuria without elevated creatinine [25,29] and 1 patient had elevated creatinine without significant proteinuria [32]. No kidney biopsy was performed.

Moderate hypergammaglobulinemia was reported in 8 patients, with

a median level of immunoglobulins G of 21.0 g/L [IQR 15.7–22.3]. The medians for the highest reported vascular endothelial growth factor (VEGF, available in 7 cases), interleukin (IL)-6 (available in 9 cases) and alkaline phosphatase (ALP; available in 7 cases) levels were 803 pg/mL [IQR 79.5–1647.5], 12.2 pg/mL [IQR 5.0–18.0], and 513.5 [IQR 229.8–998.3], respectively.

Regarding SJS' features, anti-SSA antibodies were positive in 9 patients (90%). Minor salivary gland biopsies were performed in 6 (60%) patients, demonstrating focal lymphocytic sialadenitis in all of them. Sicca syndrome was confirmed by dedicated salivary and/or lacrimal tests in 5 patients (50%). There was no histological evidence of lymphoma.

Regarding treatments, all patients have received corticosteroids. In 6 patients, corticosteroids were initiated at a moderate dose (≤ 1 mg/kg/day): 3 of them were complete responders (50%) whereas the others 3 were partial or non-responders (50%). Among patients who did not achieve complete response, two have received intravenous corticosteroids pulses, associated with cyclosporine in both cases. All of them responded. The last patient who did not respond to moderate-dose corticosteroids, secondarily received corticosteroids associated with the myelofibrosis-approved drug ruxolitinib (JAK 1/2 inhibitor), which has been effective on all TAFRO-related manifestations at 20 mg/day [18]. Three years after starting ruxolitinib (currently given at 10 mg/day) the patient is still in complete remission for both TAFRO syndrome and SJS.

Two patients have received intravenous corticosteroid pulses alone at 500 mg or 1 g per day from the start. One was non-responder and second line therapy was initiated with azathioprine on the first flare-up (pyrexia, anasarca, recurrence of lymph nodes) and with prednisolone, rituximab, tocilizumab and cyclosporine after the second flare-up, with good response [31]. The other was partial-responder and a second line therapy with cyclosporine was initiated with a good response [26]. In one case, corticosteroids (unknown dose) associated with rituximab were initiated as 1st line therapy but were inefficient. Siltuximab (anti-IL6 monoclonal antibody) was secondarily initiated, but the occurrence of posterior reversible encephalopathy syndrome required additional R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) therapy [30]. Finally, in one case, intravenous steroid pulses (1 gramme per day for 3 days) were administered concomitantly with cyclophosphamide followed by azathioprine with a good response and no relapse

Table 1
Key features in patients with SJS associated with TAFRO syndrome (SJS-TAFRO).

	Kojima 2011	Abdo 2014	Iwanaga 2016	Fujimoto 2017	Ueki 2017	Li 2019	Takasawa 2019	Suzuki 2020	Killian 2020	Ohta 2020
TAFRO syndrome	Major categories									
	Anasarca	+	+	+	+	+	+	+	+	+
	Thrombocytopenia	+	+	+	+	+	+	+	+	+
	Systemic inflammation	+	+	+	+	+	+	+	+	+
Minor categories	Histology of lymph nodes	+	+	+	+	+	+	+	+	+
	Reticulin myelofibrosis or increased number of megakaryocytes	ND	+	+	+	+	+	ND	+	+
	Mild organomegaly	+	+	+	+	+	+	+	+	+
	Renal insufficiency	ND	+	+	+	+	+	+	+	+
Sjögren's syndrome	Histopathology (labial salivary gland with focal lymphocytic sialadenitis)	ND	+	+	+	+	+	+	+	+
	Oral examination (unstimulated whole saliva flow rate ≤ 1 mL/min or scintigraphy)	ND	+	+	+	+	+	+	+	+
	Ocular examination (OSS ≥ 5 or Van Bijsterveld score ≥ 4 or Schirmer's test ≤ 5 mm/5 min)	ND	+	+	+	+	+	+	+	+
	Anti-SSA antibody	+	+	+	+	+	+	+	+	+
Treatments	Anti-SSB antibody	PSL	PSL	PSL, CyA	FMD, Celecoxib, PSL	PSL, CYP, AZA	PSL, Siltuximab, RTX, CYP, vincristine	PSL, CyA, Tolvaptan, eltrombopag	PSL, ruxolitinib	1 - PSL, AZA 2 - PSL, Rituximab, Tocilizumab, CyA

Abbreviations: OSS: Ocular staining score; PSL: prednisolone; AZA: azathioprine; CyA: cyclosporine A; CYP: cyclophosphamide; FMD: furosemide; ND: not determined.

[32].

4. Discussion

Despite the historical recommendation to exclude autoimmune disorders (explicitly including SJS in the 2019 updated version of the Japanese TAFRO syndrome research team diagnostic criteria) before considering TAFRO syndrome as a possible diagnosis, we have identified 10 cases of SJS-TAFRO. SJS is the most frequent autoimmune disease associated with TAFRO syndrome. Indeed, literature searches have revealed only few cases of TAFRO syndrome associated with other autoimmune diseases: systemic lupus erythematosus (SLE) (2 cases) [33,34], and rheumatoid arthritis [35] (one case). The authors' justification for adding SJS to the list of diseases to be excluded during differential diagnosis in the updated 2019 Masaki criteria, was the presence of "a considerable number of patients with Sjogren's syndrome" in their retrospective database [19]. Another explanation for this finding would be that TAFRO syndrome could be a severe form of SJS.

First of all, TAFRO syndrome and SJS are both rare diseases. The annual incidence rate of TAFRO syndrome is estimated between 0.9 and 4.9 per million of individuals in Japan and seems to be even rarer in European populations [36]. SJS affects 0.01–0.3% of the adult population worldwide [1–3]. Therefore, fortuitously finding them together seems very unlikely.

Moreover, the main features of TAFRO syndrome are not classically reported in SJS. To our knowledge anasarca has not been reported in SJS apart from cases associated with exudative (also called protein-losing) enteropathy, which have been reviewed elsewhere [37]. Interestingly, among the 18 reviewed cases, fecal alpha-1 antitrypsin clearance was inconstantly abnormal and features of TAFRO syndrome were reported. Moreover, according to a 2015 literature review, pleural effusion is occurring in <1% of the patients with SJS and was mostly reported in Europe and Japan [38]. Thrombocytopenia was reported in only 8% of the patients in a large Spanish SJS cohort [5], and up to 12% in 2 Chinese cohorts [39,40]. Apart from the classical tubulointerstitial nephritis (which is not consistent with TAFRO syndrome), renal dysfunction was reported in <5% in SJS [41]. Finally, a recent French nation-wide study (the largest of its kind) reported only 5 cases (out of a 67-million population) of SJS associated with autoimmune reticulin myelofibrosis [42]. Thus, it seems statistically unlikely to have the association of anasarca, thrombocytopenia, reticulin myelofibrosis and renal dysfunction to fortuitously occur in 10 SJS patients.

Furthermore, demographic data of SJS-TAFRO patients in our review reveal a female-to-male sex ratio of 2.3:1 which is very different from the 9:1 ratio in SJS [2], making it very unlikely for SJS to be a differential diagnosis of TAFRO syndrome whose sex ratio is close to 1 [43]. In line with this, biological features in SJS-TAFRO patients are mostly consistent with what has been described in the literature for TAFRO syndrome to date: moderate immunoglobulins G elevation (median 21 g/L) [20,43], high alkaline phosphatase (median 513.2 IU/L) [21,43], and IL-6 levels at diagnosis (median 12.2 pg/mL for a normal value <7 pg/mL) [43]. The median for the highest reported VEGF level is 803 pg/mL [IQR 79.50–1647.50], which seems greater than the reported values for TAFRO syndrome in the literature [20,43]. However, it was not always specified in the case reports whether it was plasma or serum levels, which makes the interpretation of these results difficult. Interestingly, VEGF, whose elevation is a hallmark of TAFRO syndrome flare-ups, has also been reported to be involved in SJS' pathophysiology [44], along with aberrant angiogenesis and increased atherosclerosis [44,45]. There are also evidence that VEGF-mediated angiogenesis leads to IL6 release by the bone marrow stromal cells and subsequent inflammation [46]. Moreover, Sisto et al., reported that anti-SSA antibodies were able to increase VEGF-A expression, trigger upregulation and activation of VEGF receptor-2 (VEGFR-2), and that enhanced angiogenesis was linked to increased VEGFR-2 phosphorylation in the minor salivary glands of patients with SJS [47]. Accordingly, anti-SSA antibodies are present in

Table 2
Main biological results in patients with SJS associated with TAFRO syndrome (SJS-TAFRO) at admission.

Feature (unit) [normal range]	Kojima 2011	Abdo 2014	Iwanaga 2016	Fujimoto 2017	Ueki 2017	Li 2019	Takasawa 2019	Suzuki 2020	Killian 2020	Ohta 2020 (onset/ relapse)
Hemoglobin (g/dL) [13–18]	13.6	8.1	10.2	8.5	11.5	10	13.2	12.6	11.5	15.8 / 9.9
WBC ($10^9/L$) [4–11]	9.79	5.47	37.6	5.19	5.4	15.48	9.28	8.9	4.45	8.7 / 3
Platelet count ($10^9/L$) [150–450]	102	26	126 (secondarily 30)	128 (secondarily 63)	46	74	210 (secondarily 50)	27	10	81 / 44
Creatinine ($\mu\text{mol/L}$) [62–106]	ND	141	52.8	79.2	81.8	111.7	78 (secondarily 176)	78.3	81 (secondarily 170)	91 / 97.7
Alkaline phosphatase (IU/L) [40–130]	ND	ND	741	209	ND	ND	1673	211	286	1084/436
Immunoglobulin G (mg/ dL) [600–1600]	2124	ND	1504	2333	ND	ND	1045	1643	2100	1024 / 2500
CRP (mg/L) [0–5]	5.6	210	36.7	74.5	195	ND (high)	134.3	12.6	70	257 / 12.8
IL 6 (pg/mL) [0–7]	4.86	18	12.2	6.2	ND	>5	58.6 [‡]	3	24.1 [‡]	NA / 15.1
VEGF (pg/mL) [62–707]	ND	Normal	1780	89	ND	803	1515 [‡]	42	840	NA / 70
Proteinuria	ND	+ (2.3 g/L)	–	+ (1.85 g/d)	–	+ (5 g/ L)	– (secondarily +)	+	– (secondarily +)	+ / +

Abbreviations: WBC: white blood cells; CRP: C-reactive protein; IL-6: interleukin-6; VEGF: vascular endothelial growth factor; ND: not determined; ‡: between one and three months after admission.

90% of the SJS-TAFRO cases which is higher than the usual two-thirds frequency of anti-SSA-positive SJS patients in most cohorts [2,48]. These autoantibodies are associated with extraglandular manifestations and higher European League against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) scores, higher frequency of activity in the constitutional, cutaneous, renal, hematological, and biological domains when compared to anti-SSA-negative patients [49,50]. Interestingly, autoantibodies (including anti-SSA) without a definitive autoimmune diagnosis have been reported in approximately one third of iMCD patients [51].

Pathophysiology of SJS is not completely understood, however the pivotal role of type I and type II IFN is well established [52–55]. In TAFRO syndrome, the overexpression of type I and type II IFN response genes during flares has only been recently demonstrated by Langan Pai et al., in CD8⁺ T-cells, NK cells and monocytes [56]. Interestingly, this overexpression correlated with high Interferon (IFN)- γ -induced protein 10 (IP-10) secretion, also called CXCL10 [57]. This protein is thought to be involved in the pathogenesis of TAFRO syndrome because higher levels of IP-10 were previously reported in TAFRO syndrome patients compared to patients with iMCD [58]. In SJS, IP-10 expression is high in both tears and saliva [59]. IFN- γ -stimulated glandular cells of the salivary glands are able to recruit T helper (Th) 1 lymphocytes via IP-10, which is possibly responsible for further enhancement of IFN- γ and IP-10 production, hence creating an amplification loop and perpetuating the autoimmune process [60]. Interestingly, one case of SJS-TAFRO has been successfully treated with ruxolitinib, a JAK1/2 inhibitor able to inhibit type I and type II IFN signaling.

In addition, abnormal B cell activation (including B-cell infiltrates within the affected organs and autoantibody production) is also a key pathogenic feature in SJS and B cell-activating factor (BAFF) is highly dependent on expression of type I and type II IFNs [2,10,61,62]. Consistent with the role of mammalian Target Of Rapamycin (mTOR) in B cell development and function [63], mTOR activity appears to be increased in infiltrating B cells within the salivary glands in SJS [64]. *Ex vivo*, rapamycin effectively blocks the proliferation and immunoglobulin production in SJS [64]. Shah et al., have also reported the efficacy of blocking mTOR pathway in reducing lymphocytic infiltration of the lacrimal glands in a mouse model of SJS [65]. These data suggest that mTOR might be an important pathway in the development of SJS and a novel potential therapeutic strategy for this disease [66]. Regarding TAFRO syndrome, a study including three IL-6 blockade-refractory

iMCD patients revealed increased CD8⁺ T cell activation, VEGF-A, and PI3K/Akt/mTOR pathway activity, whereas mTOR inhibitors attenuated CD8⁺ T cell activation and decreased VEGF-A levels, and induced clinical benefit responses in all 3 patients [67]. Langan Pai et al., reported that IFN- β stimulation of monocytes and T cells from inactive TAFRO patients, induced increased mTOR activation compared with healthy donors. This was abrogated with either mTORC1 or JAK1/2 inhibition, supporting a potentially novel role for IFN-I signaling as a driver of increased mTOR signaling in TAFRO syndrome [56]. Links were also described between IL-6 and mTOR [68], and both were abrogated with JAK1/2 inhibition [56]. In line with these findings, a clinical trial evaluating mTOR inhibitors in iMCD is ongoing (NCT03933904). None of the cases included in this review have received mTOR inhibitors, and the only approved drug for iMCD, siltuximab, has been unsuccessfully initiated in only one patient [30].

Finally, T cells seem to be involved in both diseases and the interaction between CD4⁺ T cells and B cells appears to be a key step in the development of SJS [69,70] and TAFRO syndrome [71]. Accordingly, treatment with cyclosporine, which selectively inhibits calcineurin, and thereby impairs the transcription of IL-2 and several other cytokines in T lymphocytes, seems to be relevant in cases of SJS-TAFRO [24,26,29,31]. Overall, the vast majority of the cases included in this review have been treated in a manner similar to SJS, including corticosteroids \pm immunosuppressants.

This review necessarily has limits because of its retrospective character and the rarity of the diseases of interest, leading to a small number of reported patients and the presence of missing data. We have identified ten cases of SJS-TAFRO in the literature, however this amount is probably underestimated. First, because TAFRO syndrome is a recently described entity. Secondly because in most sets of criteria (including the most recent one), any autoimmune diseases had to be ruled-out to affirm a diagnosis of TAFRO syndrome. Finally due to the severity of TAFRO syndrome and the constant need for treatment, looking for an additional diagnosis such as SJS, may be considered as futile.

5. Conclusion

The review of the literature revealed ten cases of SJS associated with TAFRO syndrome, despite the rarity of both syndromes. The description of shared immunological features (especially anti-SSA autoantibodies) and abnormal cytokine signaling pathways (e.g., interferons...) between

SjS and TAFRO syndrome could reflect the existence of pathophysiological links between these two diseases, potentially identifying TAFRO syndrome as severe manifestation of SjS, which appears to be usually managed as such. Further studies regarding this association could bring novel insights to help physicians in the therapeutic management of both diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74:1983–9. <https://doi.org/10.1136/annrheumdis-2014-205375>.
- Mariette X, Criswell LA. Primary Sjögren's syndrome. *N Engl J Med* 2018;378: 931–9. <https://doi.org/10.1056/NEJMcip1702514>.
- Psianou K, Panagoulas I, Papanastasiou AD, de Lastic A-L, Rodi M, Spantidea PI, et al. Clinical and immunological parameters of Sjögren's syndrome. *Autoimmun Rev* 2018;17:1053–64. <https://doi.org/10.1016/j.autrev.2018.05.005>.
- Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev* 2003;2:119–25. [https://doi.org/10.1016/s1568-9972\(03\)00006-5](https://doi.org/10.1016/s1568-9972(03)00006-5).
- Ramos-Casals M, Brito-Zerón P, Solans R, Camps M-T, Casanovas A, Sopena B, et al. Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: analysis of 921 Spanish patients (GEAS-SS registry). *Rheumatology (Oxford)* 2014;53:321–31. <https://doi.org/10.1093/rheumatology/ ket349>.
- Borensztein I, Ansari H, Siami-Namini K, Newman KA. Sjögren's syndrome: an undiagnosed etiology for facial pain case series with review of neurological manifestation of Sjögren syndrome. *Autoimmun Rev* 2021;20:102762. <https://doi.org/10.1016/j.autrev.2021.102762>.
- Sambataro G, Ferro F, Orlandi M, Sambataro D, Torrisi SE, Quartuccio L, et al. Clinical, morphological features and prognostic factors associated with interstitial lung disease in primary Sjögren's syndrome: a systematic review from the Italian Society of Rheumatology. *Autoimmun Rev* 2020;19:102447. <https://doi.org/10.1016/j.autrev.2019.102447>.
- François H, Mariette X. Renal involvement in primary Sjögren syndrome. *Nat Rev Nephrol* 2016;12:82–93. <https://doi.org/10.1038/nrneph.2015.174>.
- Goulabchand R, Malafaye N, Jacot W, Witkowski Durand Viel P, Morel J, Lukas C, et al. Cancer incidence in primary Sjögren's syndrome: Data from the French hospitalization database. *Autoimmun Rev* 2021;20:102987. <https://doi.org/10.1016/j.autrev.2021.102987>.
- Goules AV, Tzioufas AG. Primary Sjögren's syndrome: clinical phenotypes, outcome and the development of biomarkers. *Autoimmun Rev* 2016;15:695–703. <https://doi.org/10.1016/j.autrev.2016.03.004>.
- Nocturne G, Mariette X. Sjögren syndrome-associated lymphomas: an update on pathogenesis and management. *Br J Haematol* 2015;168:317–27. <https://doi.org/10.1111/bjh.13192>.
- Masaki Y, Kawabata H, Takai K, Kojima M, Tsukamoto N, Ishigaki Y, et al. Proposed diagnostic criteria, disease severity classification and treatment strategy for TAFRO syndrome, 2015 version. *Int J Hematol* 2016;103:686–92. <https://doi.org/10.1007/s12185-016-1979-1>.
- Takai K, Nikkuni K, Shibuya H, Hashidate H. Thrombocytopenia with mild bone marrow fibrosis accompanied by fever, pleural effusion, ascites and hepatosplenomegaly. *Rinsho Ketsueki* 2010;51:320–5.
- Louis C, Vijgen S, Samii K, Chalandon Y, Terriou L, Launay D, et al. TAFRO syndrome in Caucasians: a case report and review of the literature. *Front Med* 2017;4. <https://doi.org/10.3389/fmed.2017.00149>.
- van Rhee F, Voorhees P, Dispenzieri A, Fosså A, Srkalovic G, Ide M, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. *Blood* 2018;132:2115–24. <https://doi.org/10.1182/blood-2018-07-862334>.
- Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood* 2017;129:1646–57. <https://doi.org/10.1182/blood-2016-10-746933>.
- Kawabata H, Takai K, Kojima M, Nakamura N, Aoki S, Nakamura S, et al. Castleman-Kojima disease (TAFRO syndrome): a novel systemic inflammatory disease characterized by a constellation of symptoms, namely, thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly: a status report and summary of Fukushima (6 June, 2012) and Nagoya meetings (22 September, 2012). *J Clin Exp Hematop JCEH* 2013;53:57–61. <https://doi.org/10.3960/jslr.53.57>.
- Killian M, Viel S, Chalayer E, Forest F, Grange S, Bonnefoy P-B, et al. JAK1/2 inhibition in severe TAFRO syndrome: a case report. *Ann Intern Med* 2021;174: 719–21. <https://doi.org/10.7326/L20-1051>.
- Masaki Y, Kawabata H, Takai K, Tsukamoto N, Fujimoto S, Ishigaki Y, et al. 2019 updated diagnostic criteria and disease severity classification for TAFRO syndrome. *Int J Hematol* 2020;111:155–8. <https://doi.org/10.1007/s12185-019-02780-1>.
- Fujimoto S, Sakai T, Kawabata H, Kurose N, Yamada S, Takai K, et al. Is TAFRO syndrome a subtype of idiopathic multicentric Castleman disease? *Am J Hematol* 2019;94:975–83. <https://doi.org/10.1002/ajh.25554>.
- Nishimura Y, Fajgenbaum DC, Pierson SK, Iwaki N, Nishikori A, Kawano M, et al. Validated international definition of the thrombocytopenia, anasarca, fever, reticulocytosis, renal insufficiency, and organomegaly clinical subtype (TAFRO) of idiopathic multicentric Castleman disease. *Am J Hematol* 2021;96:1241–52. <https://doi.org/10.1002/ajh.26292>.
- Calixto O-J, Franco J-S, Anaya J-M. Lupus mimickers. *Autoimmun Rev* 2014;13: 865–72. <https://doi.org/10.1016/j.autrev.2014.05.002>.
- Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, del Pino-Montes J, et al. Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine (Baltimore)* 2008;87:210–9. <https://doi.org/10.1097/MD.0b013e318181e6af>.
- Iwanaga N, Harada K, Tsuji Y, Kawahara C, Kurohama K, Izumi Y, et al. TAFRO syndrome with primary Sjögren's syndrome. *Nihon Rinsho Meneki Gakkai Kaishi* 2016;39:478–84. <https://doi.org/10.2177/jsci.39.478>.
- Fujimoto S, Kawabata H, Kurose N, Kawanami-Iwao H, Sakai T, Kawanami T, et al. Sjögren's syndrome manifesting as clinicopathological features of TAFRO syndrome. *Medicine (Baltimore)* 2017;96. <https://doi.org/10.1097/MD.00000000000009220>.
- Takasawa N, Sekiguchi Y, Takahashi T, Muryoi A, Satoh J, Sasaki T. A case of TAFRO syndrome, a variant of multicentric Castleman's disease, successfully treated with corticosteroid and cyclosporine A. *Mod Rheumatol* 2019;29:198–202. <https://doi.org/10.1080/14397595.2016.1206243>.
- Abdo LA. First European case of TAFRO syndrome associated with Sjögren disease. *Am J Intern Med* 2014;2:102. <https://doi.org/10.11648/j.ajim.20140206.12>.
- Kojima M, Nakamura N, Tsukamoto N, Yokohama A, Itoh H, Kobayashi S, et al. Multicentric Castleman's disease representing effusion at initial clinical presentation: clinicopathological study of seven cases. *Lupus* 2011;20:44–50. <https://doi.org/10.1177/0961203310381510>.
- Suzuki E, Ichimura T, Kimura S, Kanno T, Migita K. Primary Sjögren's syndrome accompanied by clinical features of TAFRO syndrome. *Case Rep Rheumatol* 2020; 2020:8872774. <https://doi.org/10.1155/2020/8872774>.
- Li ZY, Kim S, Huang S, Mian R. Multicentric Castleman disease with TAFRO syndrome and Sjögren's. *Clin Case Rep* 2019;7:2388–92. <https://doi.org/10.1002/ccr3.2502>.
- Ohta T, Oda N, Saito K, Tamiya S, Ueno T. A case of repeated TAFRO syndrome-like symptoms and retroperitoneal hemorrhage in a patient with Sjögren syndrome. *Cureus* 2020;12:e12175. <https://doi.org/10.7759/cureus.12175>.
- Ueki M, Kobayashi I, Tozawa Y, Konishi S, Takezaki S, Okamoto T, et al. Anasarca as the initial symptom in a Japanese girl with Sjögren's syndrome. *Mod Rheumatol Case Rep* 2017;1:104–7. <https://doi.org/10.1080/24725625.2017.1282037>.
- Hasegawa E, Sato H, Wada Y, Takai K, Wakamatsu A, Nozawa Y, et al. Characterization of patients with systemic lupus erythematosus who meet the diagnostic criteria for TAFRO syndrome. *Lupus* 2018;27:417–27. <https://doi.org/10.1177/0961203317725589>.
- Tokunaga M, Yamada M, Yoshikawa S, Kondo A, Mishima M, Inoue S, et al. Systemic lupus erythematosus with marked eosinophilia and clinical features mimicking TAFRO syndrome. *Rinsho Ketsueki* 2018;59:688–94. <https://doi.org/10.11406/rinketsu.59.688>.
- Kadoba K, Waki D, Nishimura K, Mukoyama H, Saito R, Murabe H, et al. Development of severe thrombocytopenia with TAFRO syndrome-like features in a patient with rheumatoid arthritis treated with a Janus kinase inhibitor. *Medicine (Baltimore)* 2020;99:e22793. <https://doi.org/10.1097/MD.00000000000022793>.
- Masaki Y, Kawabata H, Fujimoto S, Kawano M, Iwaki N, Kotani T, et al. Epidemiological analysis of multicentric and unicentric Castleman disease and TAFRO syndrome in Japan. *J Clin Exp Hematop JCEH* 2019;59:175–8. <https://doi.org/10.3960/jslr.19021>.
- de Carvalho JF, Lerner A, Gonçalves CM, Shoenfeld Y. Sjögren syndrome associated with protein-losing enteropathy: case-based review. *Clin Rheumatol* 2021;40: 2491–7. <https://doi.org/10.1007/s10067-020-05487-5>.
- Ma D, Lu H, Qu Y, Wang S, Ying Y, Xiao W. Primary Sjögren's syndrome accompanied by pleural effusion: a case report and literature review. *Int J Clin Exp Pathol* 2015;8:15322–7.
- Aoki A, Ohno S, Ueda A, Ideguchi H, Ohkubo T, Hagiwara E, et al. Hematological abnormalities of primary Sjögren's syndrome. *Nihon Rinsho Meneki Gakkai Kaishi* 2000;23:124–8. <https://doi.org/10.2177/jsci.23.124>.
- Dai F, Yang G, Rao P, Wu P, Chen R, Sun Y, et al. Clinical characteristics of secondary immune thrombocytopenia associated with primary Sjögren's syndrome. *Front Med* 2020;7:138. <https://doi.org/10.3389/fmed.2020.00138>.
- Ramos-Casals M, Brito-Zerón P, Seror R, Bootsma H, Bowman SJ, Dörner T, et al. Characterization of systemic disease in primary Sjögren's syndrome: EULAR-SS task force recommendations for articular, cutaneous, pulmonary and renal involvements. *Rheumatology (Oxford)* 2015;54:2230–8. <https://doi.org/10.1093/rheumatology/kev200>.
- Mertz P, Chalayer E, Amoura Z, Cathebras P, Chiche L, Coestedoat N, et al. Clinical spectrum and therapeutic management of auto-immune myelofibrosis: a nationwide study of 30 cases. *Haematologica* 2021;106:871–4. <https://doi.org/10.3324/haematol.2020.249896>.
- Iwaki N, Fajgenbaum DC, Nabel CS, Gion Y, Kondo E, Kawano M, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol* 2016;91:220–6. <https://doi.org/10.1002/ajh.24242>.

- [44] Lisi S, Sisto M, D'Amore M, Lofrumento DD, Ribatti D. Emerging avenues linking inflammation, angiogenesis and Sjögren's syndrome. *Cytokine* 2013;61:693–703. <https://doi.org/10.1016/j.cyto.2012.12.021>.
- [45] Bartoloni E, Alunno A, Cafaro G, Valentini V, Bistoni O, Bonifacio AF, et al. Subclinical atherosclerosis in primary Sjögren's syndrome: does inflammation matter? *Front Immunol* 2019;10:817. <https://doi.org/10.3389/fimmu.2019.00817>.
- [46] Lee H, Lee Y, Lo A, Powell L, Shah B. Primarily VEGF-driven etiopathogenesis of TAFRO syndrome and fibroblastic reticular cells as a probable castleman cell - qualitative metasyntesis. *Blood* 2020;136:27–8. <https://doi.org/10.1182/blood-2020-137338>.
- [47] Sisto M, Lisi S, Lofrumento DD, D'Amore M, Frassanito MA, Ribatti D. Sjögren's syndrome pathological neovascularization is regulated by VEGF-A-stimulated TACE-dependent crosstalk between VEGFR2 and NF- κ B. *Genes Immun* 2012;13: 411–20. <https://doi.org/10.1038/gene.2012.9>.
- [48] Bowman S. Primary Sjögren's syndrome. *Lupus* 2018;27:32–5. <https://doi.org/10.1177/0961203318801673>.
- [49] Brito-Zerón P, Acar-Denizli N, Ng W-F, Zeher M, Rasmussen A, Mandl T, et al. How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren big data project). *Clin Exp Rheumatol* 2018;36(Suppl. 112):102–12.
- [50] Quartuccio L, Baldini C, Bartoloni E, Priori R, Carubbi F, Corazza L, et al. Anti-SSA/SSB-negative Sjögren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution. *Autoimmun Rev* 2015;14: 1019–22. <https://doi.org/10.1016/j.autrev.2015.07.002>.
- [51] Liu AY, Nabel CS, Finkelman BS, Ruth JR, Kurzrock R, van Rhee F, et al. Idiopathic multicentric Castleman's disease: a systematic literature review. *Lancet Haematol* 2016;3:e163–75. [https://doi.org/10.1016/S2352-3026\(16\)00006-5](https://doi.org/10.1016/S2352-3026(16)00006-5).
- [52] Yao Y, Liu Z, Jallal B, Shen N, Rönnblom L. Type I interferons in Sjögren's syndrome. *Autoimmun Rev* 2013;12:558–66. <https://doi.org/10.1016/j.autrev.2012.10.006>.
- [53] Nezos A, Gravani F, Tassidou A, Kapsogeorgou EK, Voulgarelis M, Koutsilieris M, et al. Type I and II interferon signatures in Sjögren's syndrome pathogenesis: contributions in distinct clinical phenotypes and Sjögren's related lymphomagenesis. *J Autoimmun* 2015;63:47–58. <https://doi.org/10.1016/j.jaut.2015.07.002>.
- [54] Soret P, Le Dantec C, Desvaux E, Foulquier N, Chassagnol B, Hubert S, et al. A new molecular classification to drive precision treatment strategies in primary Sjögren's syndrome. *Nat Commun* 2021;12:3523. <https://doi.org/10.1038/s41467-021-23472-7>.
- [55] Hall JC, Casciola-Rosen L, Berger AE, Kapsogeorgou EK, Cheadle C, Tzioufas AG, et al. Precise probes of type II interferon activity define the origin of interferon signatures in target tissues in rheumatic diseases. *Proc Natl Acad Sci U S A* 2012; 109:17609–14. <https://doi.org/10.1073/pnas.1209724109>.
- [56] Pai R-AL, Japp AS, Gonzalez M, Rasheed RF, Okumura M, Arenas D, et al. Type I IFN response associated with mTOR activation in the TAFRO subtype of idiopathic multicentric Castleman disease. *JCI Insight* 2020;5. <https://doi.org/10.1172/jci.insight.135031>.
- [57] Antonelli A, Ferrari SM, Giuggioli D, Ferrannini E, Ferri C, Fallahi P. Chemokine (C-X-C motif) ligand (CXCL)10 in autoimmune diseases. *Autoimmun Rev* 2014;13: 272–80. <https://doi.org/10.1016/j.autrev.2013.10.010>.
- [58] Iwaki N, Gion Y, Kondo E, Kawano M, Masunari T, Moro H, et al. Elevated serum interferon γ -induced protein 10 kDa is associated with TAFRO syndrome. *Sci Rep* 2017;7:42316. <https://doi.org/10.1038/srep42316>.
- [59] Chen X, Aqrabi LA, Utheim TP, Tashbayev B, Utheim ØA, Reppe S, et al. Elevated cytokine levels in tears and saliva of patients with primary Sjögren's syndrome correlate with clinical ocular and oral manifestations. *Sci Rep* 2019;9:7319. <https://doi.org/10.1038/s41598-019-43714-5>.
- [60] Dufour JH, Dziejman M, Liu MT, Leung JH, Lane TE, Luster AD. IFN-gamma-inducible protein 10 (IP-10; CXCL10)-deficient mice reveal a role for IP-10 in effector T cell generation and trafficking. *J Immunol Baltim Md* 1950;2002(168): 3195–204. <https://doi.org/10.4049/jimmunol.168.7.3195>.
- [61] Varin M-M, Le Pottier L, Youinou P, Saulep D, Mackay F, Pers J-O. B-cell tolerance breakdown in Sjögren's syndrome: focus on BAFF. *Autoimmun Rev* 2010;9:604–8. <https://doi.org/10.1016/j.autrev.2010.05.006>.
- [62] Möckel T, Basta F, Weinmann-Menke J, Schwarting A. B cell activating factor (BAFF): structure, functions, autoimmunity and clinical implications in systemic lupus erythematosus (SLE). *Autoimmun Rev* 2021;20:102736. <https://doi.org/10.1016/j.autrev.2020.102736>.
- [63] Fruman DA, Limon JJ. Akt and mTOR in B cell activation and differentiation. *Front Immunol* 2012;3. <https://doi.org/10.3389/fimmu.2012.00228>.
- [64] Blokland SLM, Hillen MR, Wichers CGK, Zimmermann M, Kruijze AA, Radstake TRDJ, et al. Increased mTORC1 activation in salivary gland B cells and T cells from patients with Sjögren's syndrome: mTOR inhibition as a novel therapeutic strategy to halt immunopathology? *RMD Open* 2019;5:e000701. <https://doi.org/10.1136/rmdopen-2018-000701>.
- [65] Shah M, Edman MC, Janga SR, Shi P, Dhandhukia J, Liu S, et al. A rapamycin-binding protein polymer nanoparticle shows potent therapeutic activity in suppressing autoimmune dacryoadenitis in a mouse model of Sjögren's syndrome. *J Control Release Off J Control Release Soc* 2013;171:269–79. <https://doi.org/10.1016/j.jconrel.2013.07.016>.
- [66] Geier C, Perl A. Therapeutic mTOR blockade in systemic autoimmunity: implications for antiviral immunity and extension of lifespan. *Autoimmun Rev* 2021;20:102984. <https://doi.org/10.1016/j.autrev.2021.102984>.
- [67] Fajgenbaum DC, Langan R-A, Japp AS, Partridge HL, Pierson SK, Singh A, et al. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. *J Clin Invest* 2019;130: 4451–63. <https://doi.org/10.1172/JCI126091>.
- [68] Arenas DJ, Floess K, Kobrin D, Pai R-AL, Srkalovic MB, Tamakloe M-A, et al. Increased mTOR activation in idiopathic multicentric Castleman disease. *Blood* 2020;135:1673–84. <https://doi.org/10.1182/blood.2019002792>.
- [69] Voulgarelis M, Tzioufas AG. Pathogenetic mechanisms in the initiation and perpetuation of Sjögren's syndrome. *Nat Rev Rheumatol* 2010;6:529–37. <https://doi.org/10.1038/nrrheum.2010.118>.
- [70] Felten R, Scher F, Sibilia J, Gottenberg J-E, Arnaud L. The pipeline of targeted therapies under clinical development for primary Sjögren's syndrome: a systematic review of trials. *Autoimmun Rev* 2019;18:576–82. <https://doi.org/10.1016/j.autrev.2018.12.008>.
- [71] Kurose N, Guo X, Shioya A, Mizutani K-I, Kumagai M, Fujimoto S, et al. The potential role of follicular helper T cells in idiopathic multicentric Castleman disease with and without TAFRO syndrome. *Pathol Res Pract* 2019;215:152563. <https://doi.org/10.1016/j.prp.2019.152563>.