Immunologic Research (2022) 70:19–22
https://doi.org/10.1007/s12026-021-09243-y

REVIEW

Plummer-Vinson syndrome in primary Sjögren syndrome: a case-based review

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Received: 14 June 2021 / Accepted: 7 October 2021 / Published online: 14 October 2021

Abstract

This study aimed to describe a patient with Sjögren syndrome who developed Plummer-Vinson syndrome, and to review the literature and describe shared aspects of this rare association. A systematic screening of articles was conducted in PubMed/MEDLINE, LILACS, SciELO, Scopus, Web of Science, and Cochrane, dating 1940 to 2020. All the articles included the association between Sjögren syndrome and Plummer-Vinson syndrome. No language restriction was applied. The following terms were used: "Sjögren syndrome" or "sicca syndrome" and "Plummer-Vinson syndrome" or "Paterson-Kelly syndrome." We performed our analysis by adding our present case, with a total of 4 cases. Three out of four were female (75%), age varied from 56 to 58 years old. In 2 cases, Sjögren syndrome preceded Plummer-Vinson syndrome diagnosis, and in 1 report, Plummer-Vinson syndrome appeared before Sjögren syndrome. Disease duration varied from 7 to 20 years. In two cases, autoantibodies were available, and antinuclear antibodies and anti-Ro/SS-A were positive in both, and anti-La/SS-B in one of them was associated with anti-dsDNA; however, no data regarding lupus was available in the article. Treatment involved iron supplementation in 3/3. Two out of three received parenteral iron supplementation, and in these two cases, mechanical esophageal dilatation was needless. In the other case, an additional endoscopic esophageal dilatation was necessary to receive the oral iron supplement. All 3 cases had a good outcome. This case illustrates a patient with Sjögren syndrome who developed the rare Plummer-Vinson syndrome. In Sjögren syndrome, the presence of iron-deficiency anemia, dysphagia, and weight loss should alert the physician to search for associated Plummer-Vinson syndrome.

Highlights

- Plummer-Vinson syndrome (PVS) is a sporadic disease characterized by the triad of dysphagia, iron-deficient anemia, and webs on the esophagus.
- There are only three previous cases of PVS in Sjögren syndrome.
- The parenteral iron supplementation treats PVS adequately and seems to preclude the need for endoscopic esophageal dilatation.

Keywords Plummer-Vinson syndrome · Paterson-Kelly syndrome · Anemia · Iron-deficiency anemia · Dysphagia · Sjögren syndrome

Introduction

Sjögren syndrome (SS) is an autoimmune exocrinopathy mainly characterized by dryness of the eyes and mouth due to lacrimal and salivary glands' involvement. Besides the gland impairment, SS patients may have systemic manifestations such as fever and weight loss and organ and systemic involvement, leading to neurological, pulmonary, and hematological disorders [1].

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Regarding hematological disorders, leucopenia, lymphoproliferative diseases such as lymphoma in 5 to 10% of the SS cases, and anemia are common complications in SS patients. Anemia may be due to hemolysis present in less than 5% of the cases, thrombocytopenia in less than 5%, and anemia due to iron deficiency or chronic inflammation in 9% of the cases [1, 2]. On the other hand, a rare complication linked to iron deficiency anemia is the Plummer-Vinson syndrome (PVS). This disorder presents a triad of iron deficiency anemia, dysphagia, and esophageal stenosis. Very few cases of PVS were described in SS patients, and most of the articles were published decades ago; the most recent one appeared in 2011 [3–6].

The purpose of this article is to review the literature on this rare association, adding a new case report that was successfully treated with intramuscular iron supplementation. Additionally, interrelationship and shared aspects between SS and PVS are discussed.

Methods

Patient selection

The present research is characterized as a descriptive and cross-transversal study with a retrospective analysis of the medical records of a patient diagnosed with both SS and PVS. An informed consent was obtained from the patient.

Literature review

A systematic screen of articles published in PubMed/MEDLINE, LILACS, SciELO, Scopus, Web of Science, and Cochrane dating from 1940 to August 2020 was performed. The following terms were used: "Sjögren syndrome" or "sicca syndrome" and "Plummer-Vinson syndrome" or "Paterson-Kelly syndrome." The screen did not have restrictions on languages. Also, a new case report with the association mentioned above is described in detail. Two authors independently reviewed the articles. The following information was collected: demographic characteristics (sex, age), clinical and laboratory features (clinical presentation, autoantibodies, the onset of symptoms and progression), therapy provided, and response to reported therapy. A thorough analysis of each of these 3 scientific articles and their list of references was conducted. Duplicate articles, insufficiently detailed or not informative enough, were excluded.

Case report

A 57-year-old female patient presented with progressive dysphagia for solids, associated with weight loss since 2004. She had a past medical history of low-meat consumption and severe hypermenorrhea with chronic anemia for more than 20 years, which led to total hysterectomy at 44 years old. Due to swallowing difficulties, an upper endoscopy showed upper esophageal stenosis due to a typical esophageal web. A cervical and thorax tomography confirmed the esophageal narrowing and the web. Laboratory test revealed hemoglobin of 7.2 g/dL (12–16 g/dL), hematocrit of 21.6% (36–48%), iron of 20 mcg/dL (75–150 mcg/dL), ferritin of 5 ng/mL (11–306 ng/mL), and transferrin saturation of 8% (20–55%). In 2005, a diagnosis of Plummer-Vinson syndrome was determined based on the classical triad of dysphagia, iron-deficiency anemia, and a web in the esophagus. Further tests revealed positive antinuclear antibodies with a titer of 1:640, and anti-Ro/SS-A antibodies. Anti-dsDNA, anti-Sm, and anti-La/SS-B were all negative, but vitamin B12 was deficient 200 pg/mL (> 300 pg/mL). Since she had a long-term history of xerophthalmia and xerostomia, and a positive Schirmer test < 5 mm in 5 min and Bengal rose with a positive score of > 6, positive ANA, and anti-Ro/SS-A, a SS diagnosis was determined in 2011. She denied a salivary minor gland biopsy. Peroral iron sulfate 50 mg twice a day was started, but she had difficulty swallowing the capsules and had gastric intolerance. Prednisone 20 mg/day for 60 days, omega-3 2 g (she drank the content of the capsule), and artificial tears were initiated. Oral water increase and artificial saliva were suggested, but no improvement in dysphagia was noted. She refused hydroxychloroquine use. To treat her nutritional deficiencies, a weekly intramuscular injection of iron hydroxide saccharate 100 mg and cyanocobalamin 5000 mcg for 4 weeks was started and then tapered off to every 3 months since she still could not swallow the iron pills. After 3 months, she experienced a marked improvement in her clinical picture. Her dysphagia improved, her complete blood count and iron storage parameters had normalized (hemoglobin 13 g/dL, hematocrit 39%, iron 80 mcg/dL, ferritin 80 ng/mL), and vitamin B12 was within normal range 600 pg/mL. Currently, she is well, although xerophthalmia is present. She is on omega-3 2 g/day to improve lacrimal quality and intramuscular iron every 3 months. The patient denied to repeat the upper endoscopy for follow-up.

Results

Table 1 summarizes the patients reported with this rare association between SS and PVS. The literature searching found 8 articles, and the abstract reading excluded 4 of them. We could not find one article since it was old (the year 1951), and no contact was available. In the end, we have 3 articles with 3 patients with SS and PVS [3, 4, 6]. We performed our analysis by adding our present case, with a total of 6 cases.

Table 1 Summary of the patients reported with this rare association between SS and PVS

Author (year)	*N*, sex, age (years old)	Disease sequence	Disease duration	SS-related antibodies	PVS characteristics	Treatment	Outcome
Carvalho et al., 2020 (present article)	1, female, 57	PVS ➔ SS	7 years	ANA Anti-Ro/SS-A	Dysphagia, Hb 7.2 g/dL	Intramuscular iron supplementation	Good
Ouakaa-Kchaou et al., 2011	1, female, 56	PVS ➔ SS	20 years	ANA Anti-Ro/SS-A Anti-La/SS-B Anti-dsDNA	Dysphagia, Hb 6.8 g/dL due to hypermenorrhea	Esophageal dilatation Oral iron supplementation	Good
Doig JA et al., 1971	1, male, 58	N/A	N/A	N/A	Dysphagia, anemia (Hb 12.9 g/dL), but the iron profile was normal, cheilitis, lingual papillae atrophy	N/A	N/A
Godtfredsen E, 1947	3*, female, 56 (mean)	SS ➔ PVS	11 years (mean)	N/A	Dysphagia, Hb 6.5–9.0 g/dL	Parenteral iron associated with riboflavin	Recovered in 15–25 days

SS, Sjögren syndrome; *PVS*, Plummer-Vinson syndrome; *N/A*, not available

*These 3 cases were confirmed by esophagogram imaging

Three out of six were female (50%), and age varied from 56 to 58 years old [3, 4, 6]. In 2 cases, PVS preceded SS diagnosis [3]; in 1 report, SS appeared before PVS [4], and the last one was not available [6]. Disease duration varied from 7 to 20 years. In two cases, autoantibodies were available and antinuclear antibodies and anti-Ro/SS-A were positive in both, and anti-La/SS-B in one of them was associated with anti-dsDNA [3, 4, 6]. However, no data regarding lupus was available in the article.

Treatment involved iron supplementation in 3/3 [3, 4]. And for the other article, this datum was not available [6]. Two out of three received parenteral iron supplementation [6], and in these two cases, mechanical esophageal dilatation was needless [6]. In the other case, an additional endoscopic esophageal dilatation was necessary to receive the oral iron supplement [3]. All 6 cases had a good outcome [3, 4, 6].

Discussion

This is a rare patient report with SS who developed PVS and was successfully treated with parenteral iron supplementation.

Plummer-Vinson or Paterson-Kelly syndrome is a rare condition characterized by the triad of dysphagia, iron-deficiency anemia, and esophageal webs. It affects more commonly Caucasian middle-aged women between the fourth to seventh decades of life. Dysphagia is usually painless and intermittent or progressive over the years, limited to solids, and usually linked to weight loss. Symptoms resulting from anemia that include weakness, fatigue, tachycardia, and cutaneous pallor may dominate the clinical picture and maybe the only presentation. Additional features are glossitis, angular cheilitis, and koilonychia. Splenomegaly and enlargement of the thyroid are also reported. Although iron deficiency is the primary causal factor, pathophysiologic mechanisms are unknown, followed by malnutrition, genetic predisposition, or autoimmune processes, as verified in our patient. PVS is treated effectively with iron supplementation, and, in many cases, there is a need for esophageal mechanical dilatation [7].

The pathophysiological mechanisms of PVS are yet unknown, but they are probably multifactorial [3].

Since PVS seems to be a premalignant condition, with an increased risk of squamous cell carcinoma of the pharynx and the esophagus, the patients should be followed closely [8]. This point of neoplasia risk is critical since SS patients are prone to lymphoproliferative disorders. The presence of salivary gland enlargement, lymphadenopathy, Raynaud phenomenon, anti-Ro/SS-A or/and anti-La/SS-B autoantibodies, rheumatoid factor positivity, monoclonal gammopathy, and C4 hypocomplementemia was shown to be independent predictors for non-Hodgkin lymphoma development in SS patients [9]. Some explanations are available regarding this increased risk of lymphoma in SS and include, first, a sustained antigen drive, which could be provided by infectious agents, such as *Helicobacter pylori* and hepatitis C virus, acting independently of autoimmune expression; the second mechanism is exogenous antigens that induce autoimmune responses by molecular mimicry; and a third

alternative mechanism would be the presence of autoantigens, such as the lymphoma associated with Sjögren's syndrome (Fc of IgG) [10]. The mechanisms of cancer risk in PVS are yet very little understood.

Regarding treatment, iron supplementation was usually able to correct PVS in several reported subjects. However, due to the esophageal stenosis, the patient cannot swallow the iron pills, so the oral route was replaced by parenteral iron therapy, which was very useful. A part of PVS, patients will need an endoscopic dilatation approach, especially those with the long-term disease [11]. Supplementing iron for all patients with the web, regardless of the hemoglobin status, was suggested to replenish the iron stores [12]. The present patient had multifactorial iron-deficiency anemia mainly caused by hypermenorrhea, low-meat ingestion, and dysphagia leading to malnutrition.

Despite belonging to different disease categories, several aspects are shared between SS and PVS. Both affect the gastrointestinal tract and the esophagus [6, 12], and both are precancerous entities [9, 13]; also in PVS, there are some autoimmune aspects [11]. Interestingly, other conditions associated with esophageal webs are autoimmune disorders of the thyroid, rheumatoid arthritis, pernicious anemia, celiac disease, psoriasis, graft versus host disease, and blistering diseases of the skin [14]. Surprisingly, a web identical to that found in PVS was seen in a SS patient [6]. Finally, iron deficiency anemia is prevalent [7, 8, 11–13, 15].

Dysphagia is a relatively common symptom in SS, and it was calculated in 75% of these patients [16]. Causes for this dysphagia in SS are usually linked to xerostomia and the reduced secretions of the esophagus present in this autoimmune disease [17].

In conclusion, the present study reports a rare PVS in a patient with primary SS. It highlights the shared aspect between the two conditions, the beneficial aspect of intramuscular iron therapy, and the necessity of the early diagnosis and prompt therapy of both premalignant disorders. Furthermore, parenteral iron supplementations seem to be useful in excluding the necessity of endoscopic esophageal dilatation in the cases herein reviewed.

Author contribution JFC: conception, analysis, writing, interpretation, revision, submission.

AL: analysis, writing, interpretation, revision.

Declarations

Ethics approval The authors declare that they followed the World Medical Association Declaration of Helsinki in this study. An informed consent was obtained from the patients for publication of their cases. No image of her is used.

Conflict of interest The authors declare no competing interests.

References

1. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, Bosch X. Primary Sjogren syndrome. BMJ. 2012;344:e3821.
2. Zhou JG, Qing YF, Jiang L, Yang QB, Luo WF. Clinical analysis of primary Sjögren's syndrome complicating anemia. Clin Rheumatol. 2010;29(5):525–9.
3. Ouakaa-Kchaou A, Jebali S, Elloumi H, et al. Association d'un syndrome de Gougerot Sjögren et d'un syndrome de Plummer Vinson [Association of Sjögren's syndrome and Plummer Vinson syndrome]. Rev Med Interne. 2011;32(2):e21–2.
4. Godtfredsen E. Relation between Sjögren's disease, the Plummer-Vinson syndrome, and ariboflavinosis. Acta Ophthalmol (Copenh). 1947;25(1):95–109.
5. Charvat J. Zespół Sjögrena i Plummer-Vinsona i jego udzial w powstawaniu raka [The Sjögren and Plummer-Vinson syndrome and its role in etiology of cancer]. Pol Tyg Lek (Wars). 1951;6(37):1169–74.
6. Doig JA, Whaley K, Dick WC, Nuki G, Williamson J, Buchanan WW. Otolaryngological aspects of Sjögren's syndrome. Br Med J. 1971;4(5785):460–3.
7. Liu CC, Lin YS. Plummer-Vinson syndrome. *Ear Nose Throat J*. 2019;98(5):259–260.; Novacek G. Plummer-Vinson syndrome. *Orphanet J Rare Dis*. 2006;1:36.
8. Bakshi SS. Plummer-Vinson syndrome. Mayo Clin Proc. 2016;91(3):404.
9. Fragkioudaki S, Mavragani CP, Moutsopoulos HM. Predicting the risk for lymphoma development in Sjogren syndrome: an easy tool for clinical use. Medicine (Baltimore). 2016;95(25):e3766.
10. Mackay IR, Rose NR. Autoimmunity and lymphoma: tribulations of B cells. Nat Immunol. 2001;2(9):793–5.
11. Hefaiedh R, Boutreaa Y, Ouakaa-Kchaou A, et al. Plummer-Vinson syndrome. Tunis Med. 2010;88(10):721–4.
12. Goel A, Bakshi SS, Soni N, Chhavi N. Iron deficiency anemia and Plummer-Vinson syndrome: current insights. J Blood Med. 2017;8:175–84.
13. Novacek G. Plummer-Vinson syndrome. Orphanet J Rare Dis. 2006;1:36.
14. Dutta U, Khaliqa A, Noora MT, Kochhara R, Singh K. Recurrent multiple cervical esophageal webs: an unusual presentation of celiac disease. Gastroenterology Res. 2009;2:356–7.
15. Zhou J-G, Qing Y-F, Li Jiang, Yang Q-B, Luo W-F. Clinical analysis of primary Sjögren's syndrome complicating anemia. Clin Rheumatol. 2010;29:525–9.
16. Bécheur H, Poyet A, Delahaye F, Mostefa-Kara N. Syndrome de GougerotSjögren et achalasie. Gastroenterol Clin Biol. 2006;30:918–20.
17. Anselmino M, Zaninotto G, Costantini M, Ostuni P, Ianniello A, Boccu C. Esophageal motor function in primary Sjogren's syndrome: correlation with dysphagia and xerostomia. Dig Dis Sci. 1997;42:113–8.