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REVIEW

Primary Biliary Cholangitis Associated with Skin Disorders: A Case Report and Review of the Literature

Benedetta Terziroli Beretta-Piccoli[1] · Caroline Guillod[2] · Igor Marsteller[3] · Roland Blum[4] · Luca Mazzucchelli[5] · Chiara Mondino[2] · Pietro Invernizzi[6] · M. Eric Gershwin[7] · Carlo Mainetti[2]

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Abstract Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease. It is often associated with extrahepatic autoimmune diseases. Skin disorders are sporadically reported in association with PBC. We report an unusual case of PBC associated with acquired reactive perforating dermatosis (ARPD) and present a review of the literature on skin disorders associated with PBC. Our patient presented to the dermatology department with generalized pruritus associated with nodular perforating skin lesions on the trunk, and cholestatic liver disease of unknown origin. After having established both diagnosis of ARPD and PBC, she was managed in an interdisciplinary manner, and both her skin and liver conditions improved gradually. Only one similar case is reported in the literature, in that case, the liver disease was not treated. By reviewing the literature, we found that lichen planus, vitiligo, and psoriasis are the most frequent skin disorders associated with PBC. However, there is only limited data about specific skin disorders associated with PBC. This case report of a patient with PBC associated with ARPD underlines the importance of interdisciplinary management of patients with rare liver diseases combined with rare skin disorders. The present review of the literature shows that probably, immune-mediated skin conditions are not more frequent in PBC patients than in the general population. However, the available data are scant; there is a need for high-quality data on skin conditions associated with PBC.

Keywords Primary biliary cholangitis · Acquired reactive perforating dermatosis · Skin disorders · Case report · Review of the literature

Abbreviations

PBC	Primary Biliary Cholangitis
ARPD	Acquired reactive perforating dermatosis
AMA	Anti-mitochondrial antibodies
ANA	Anti-nuclear antibodies
UDCA	Ursodeoxycholic acid
BMI	Body mass index
ULN	Upper limit of norm
IQR	Interquartile range
ELISA	Enzyme-linked immunosorbent assay
SSY	Sjögren's syndrome
AIH	Autoimmune hepatitis
SS	Systemic sclerosis

Lab work performed at Ospedale Regionale Bellinzona, Switzerland.

✉ Benedetta Terziroli Beretta-Piccoli
benedetta.terziroli@hin.ch

✉ M. Eric Gershwin
megershwin@ucdavis.edu

[1] Epatocentro Ticino, Epatocentro Ticino, Via Soldino 5, Lugano, Switzerland

[2] Dermatologia Ente Ospedaliero Cantonale, Ospedale Regionale Bellinzona, Bellinzona, Switzerland

[3] Servizio di Gastroenterologia Ospedale Regionale Bellinzona, Bellinzona, Switzerland

[4] Dermatopathologie Labor, Dermatologische Klinik, Universität Bern, Bern, Switzerland

[5] Istututo Cantonale di Patologia, Locarno, Switzerland

[6] Program for Autoimmune Liver Diseases, International Center for Digestive Health, University of Milan-Bicocca, San Gerardo Hospital, Monza, Italy

[7] Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA

Introduction

Primary biliary cholangitis (PBC) is a rare chronic autoimmune liver disease characterized by destruction of small intrahepatic bile ducts leading to cirrhosis and eventually liver failure (Carey et al. 2015; European Association for the Study of the Liver 2009; Invernizzi 2014; Lindor et al. 2009). High titer anti-mitochondrial (AMA) and rim-like and/or nuclear dots anti-nuclear (ANA) auto-antibodies are disease-specific (Carey et al. 2015; Invernizzi et al. 2005, 2007; Lindor et al. 2009; Metcalf et al. 1997). The condition affects mainly women (Baldursdottir et al. 2012; Kim et al. 2000; Koulentaki et al. 2014; Metcalf et al. 1997), although the accepted 9–10:1 female-to-male ratio may be an overestimate (Podda et al. 2013). The etiopathogenesis is still enigmatic. A genetic predisposition likely plays an important role (Bianchi et al. 2014). Environmental factors have also been described as risk factors (Gershwin et al. 2005). The first-line treatment is ursodeoxycholic acid (UDCA), which is effective in about 70% of cases (Beuers et al. 2015i; Carbone et al. 2014; European Association for the Study of the Liver 2009; Lindor et al. 2009). New compounds are currently developed for patients with insufficient response to standard treatment (Beuers et al. 2015i). Among these, the farnesoid-X-receptor agonist obeticholic acid has recently been approved in USA as the second-line treatment for PBC patients with insufficient response or intolerant to UDCA (Nevens et al. 2016). The disease was formerly called primary biliary cirrhosis. As the term "cirrhosis" has the stigmata for alcohol abuse, the disease has recently been renamed "primary biliary cholangitis" (Beuers et al. 2015a, b, c, d, e, f, g, h, i). There has been an enormous body of literature on the immunopathology and molecular biology of PBC (Beuers and Gershwin 2015; Bian et al. 2015; Chang et al. 2015; Choi et al. 2015; Hirschfield and Siminovitch 2015; Huang et al. 2014; Hudspeth et al. 2016; Liberal et al. 2016; Lleo et al. 2012; Pollheimer and Fickert 2015; Sun et al. 2015; Takahashi et al. 2012; Tomiyama et al. 2015; Wang et al. 2015; Webb et al. 2015; Yang et al. 2016; Yao et al. 2014).

Acquired reactive perforating dermatosis (ARPD) is a rare disease, which belongs to the group of the primary perforating dermatoses. Its pathogenesis and aetiology are still not completely understood today. It is possible that genetic predisposition, associated diseases, and occasionally certain drugs may play a causal role. ARPD is characterized clinically by a central hyperkeratotic plug-like, depressed, necrotic papulonodular lesion, and histologically by a transepidermal elimination of basophilic collagen bundles. Itching is nearly always present as a symptom in ARPD and skin microtrauma caused by scratching can trigger in predisposed patients the development of focal degeneration of the collagen fibres (Wagner and Sachse 2013). The clinical appearance of ARPD is typical, but in the early stage disease, distinguishing it from other primary perforating dermatoses, such as hyperkeratosis follicularis et parafollicularis in cutem penetrans (Kyrle's disease), can be difficult (Wagner and Sachse 2013). The treatment is based on topical steroids, which can also be injected intra-lesionally.

We herein describe the unusual case of a 60-year-old female patient with PBC associated with ARPD.

Case Report

A 60-year-old Caucasian lady presented with generalized pruritus and fatigue which had gradually worsened over the last 6 months. Her medical history was remarkable for diabetes mellitus type II since 7 years and arterial hypertension. She was on metformin and enalapril. She did not drink alcohol. Physical examination showed overweight (BMI: 30), jaundiced sclera, and skin, as well as xerostomia and xerophthalmia. In addition, multiple erythematous nodular perforating skin lesions and excoriations (Fig. 1) were present on her trunk. Laboratory investigations showed normal renal function, a cholestatic biochemical profile, and minimally altered liver function tests: bilirubin, 42.4 µmol/l (ULN: 19 µmol/l); alkaline phosphatase, 308 U/l (ULN: 129 U/l); alanine transaminase, 76 U/l (ULN: 41 U/l); gamma glutamyl transpeptidase, 283 U/l (ULN: 61 U/l), albumin, 31 g/l (normal range 35–50 g/l): INR 0.9. Serologies for hepatitis A, B, C, and E were negative. HbA1c was 6.1%, proving that her diabetes mellitus type II was mild and well controlled with metformin mono-therapy and diet. Abdominal ultrasound and computer tomography scans showed no ascites, no focal liver lesions, no portal vein thrombosis, and no splenomegaly (11 cm). Liver transient elastography was consistent with advanced fibrosis

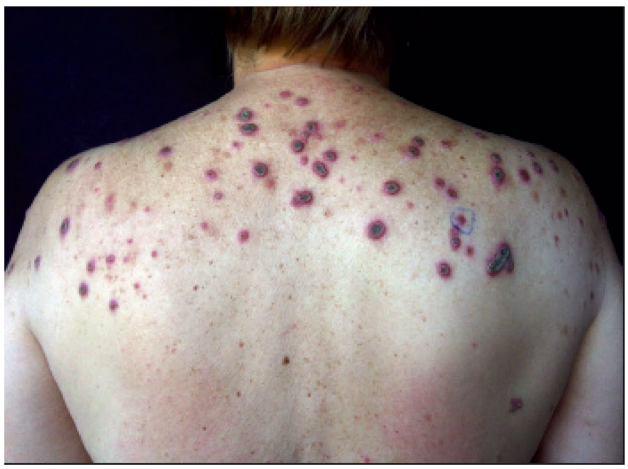

Fig. 1 Nodular perforating skin lesions on the trunk

(14.3 kPa, IQR 3.8 kPa, success rate 100%). Autoantibody testing showed positive ANA (1:320, speckled immunofluorescence pattern on Hep-2 cells) and high titer anti-mitochondrial antibodies (1:2′560 on immunofluorescence, 5565,0 U/ml on ELISA). Dot-blot for PBC-specific ANA (anti-sp100 and anti-gp210) was negative.

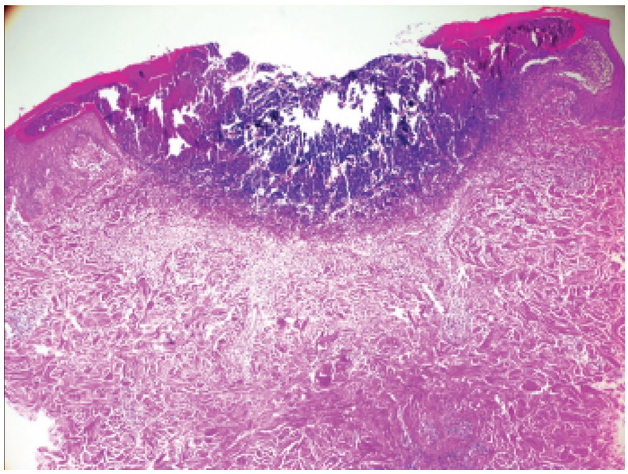

Fig. 2 Collagenous perforating dermatosis: perilesional epidermis with acanthotic spread, focal hypergranulosis, and compact ortho- and parakeratosis (HE)

Histopathological analysis of a nodular skin lesion was consistent with reactive perforating collagenosis. Perilesional epidermis showed acanthotic spread with focal hypergranulosis and compact ortho- and parakeratosis (Fig. 2).

Histopathological analysis of a liver biopsy specimen showed chronic portal hepatitis with granulomata, presence of plasma cells, and moderate bile duct damage (Fig. 3). Complete fibrotic porto-central septa were present, matching the definition of advanced fibrosis.

A salivary gland biopsy showed focal lymphocyte sialadenitis. Serum anti-SS-A antibodies were positive. Taking together the clinical findings with these results, a diagnosis of Sjögren's syndrome (SSY) was established.

Initially, ARPD-treatment was started with topical corticosteroids and intralesional injections of triamcinolone, followed by topical tretinoin. We did not observe a significant improvement of the skin lesions. 5 weeks later, PBC treatment was started with UDCA at a dosage of 13 mg/kg body weight. The biochemical cholestasis, the liver function, and the skin lesions improved gradually over a few months after the initiation of UDCA. The Child-Pugh

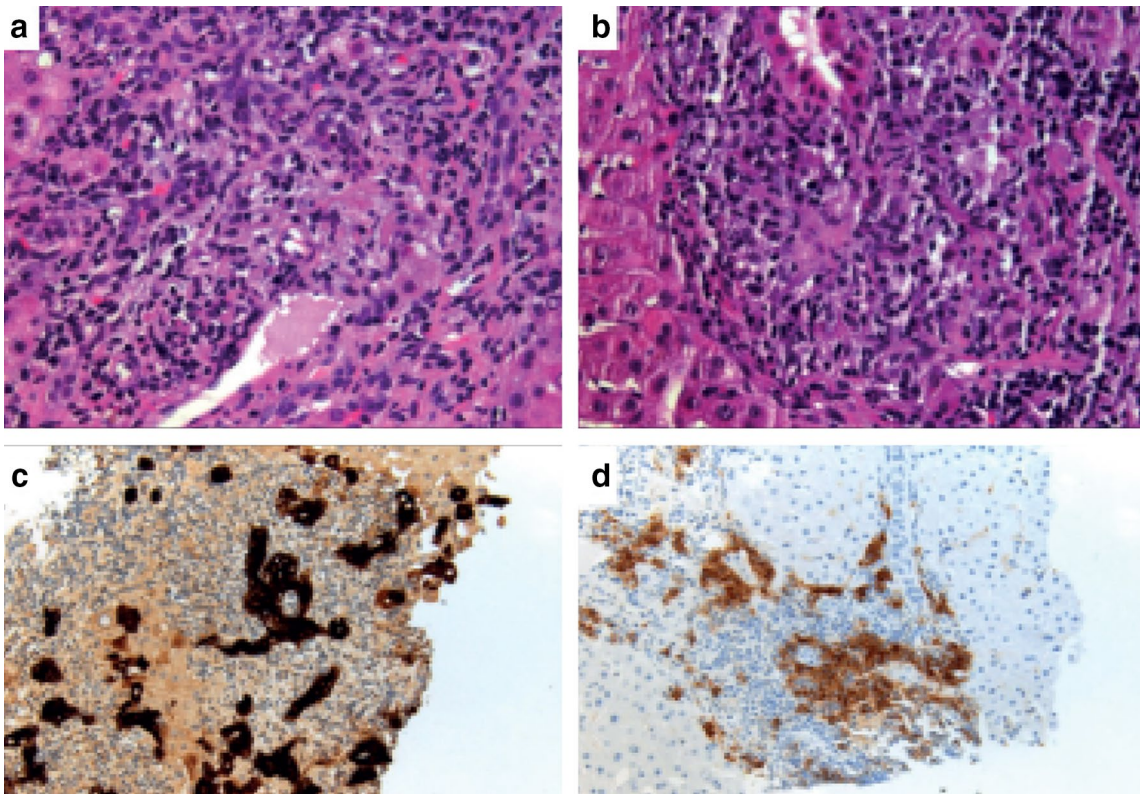

Fig. 3 Liver biopsy. **a** Portal tract with moderate inflammation and some degree of interface activity (HE). **b** Well-formed granuloma with florid duct lesions (HE). **c** Immunostain for cytokeratin 7 highlights an irregular bile duct and ductular proliferation consistent with chronic cholestasis. **d** Immunostain for CD38 shows numerous plasma cells surrounding a bile duct and at the portal tract periphery

score improved from B7 to A5 (albumin and bilirubin normalised). Despite this, the alkaline phosphatase remained elevated at about 2.5 × UPN; the severe pruritus did not improve significantly. In PBC, the absence of normalisation or near-normalisation of alkaline phosphatase is a marker of an unfavourable outcome (Carey et al. 2015). For this reason, after 6 months of UDCA mono-therapy, fenofibrate was added with success: alkaline phosphatase decreased to less than 1.5 ULN 3 months later. The pruritus disappeared and the skin lesions were healing (Fig. 4).

Discussion

We herein present a patient with a combination of two rare diseases: PBC and ARPD. The association of PBC with extrahepatic autoimmune conditions both in personal clinical history and in family history is well known (Corpechot et al. 2010; Efe et al. 2012; Floreani et al. 2015; Gershwin et al. 2005; Lammert et al. 2013; Muratori et al. 2015; Parikh-Patel et al. 2001), with reported frequency reaching 61.2% in an Italian series of 361 patients (Floreani et al. 2015). The most frequent association is with SSY, Raynaud's syndrome, and autoimmune thyroid disease (Corpechot et al. 2010; Efe et al. 2012; Floreani et al. 2015; Gershwin et al. 2005; Lammert et al. 2013; Muratori et al. 2015; Parikh-Patel et al. 2001). A concomitant extrahepatic autoimmune disease does not affect the disease course (Efe et al. 2012; Floreani et al. 2015; Muratori et al. 2015). Concomitant skin disorders have also been reported, mostly lichen planus, vitiligo, and psoriasis, but are rarer, with a reported frequency of up to 5–8% (Efe et al. 2012; Floreani et al. 2015; Gershwin et al. 2005; Muratori et al. 2015).

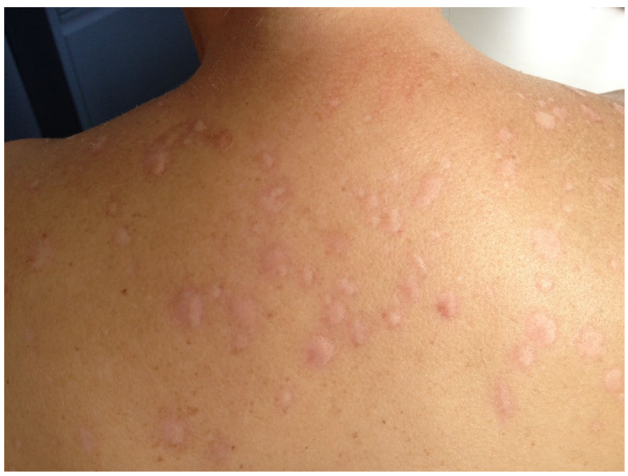

Fig. 4 Healing of the skin lesions after steroid local treatment and PBC treatment

Six cases of skin diseases from the primary perforating dermatoses group linked to autoimmune liver diseases have been reported so far. Five were linked to primary sclerosing cholangitis (Beachkofsky and Cragun 2012; Kahana et al. 1985; Mahajan et al. 2004; Roldán-Marín et al. 2009) and one to PBC (Chiu and Haley 2007). No case has been reported in association with autoimmune hepatitis (AIH). In a Korean series of 30 patients with acquired perforating dermatosis (Kim et al. 2014), two of them had associated "hepatitis", which was probably viral hepatitis. All these cases were reported by dermatologists.

The only case reported so far of PBC associated with ARPD is a female 47-year-old patient who had concomitant rheumatoid arthritis and Hashimoto's thyroiditis, without diabetes or renal failure (Chiu and Haley 2007). Treatment of PBC is not mentioned by the authors, and the skin condition did not improve substantially. We assume that PBC was not treated specifically in that case, underling that interdisciplinary management is essential. No rheumatoid arthritis or Hashimoto's thyroiditis was found in our patient, but a sicca syndrome in the context of a SSY.

ARPD is commonly associated with diabetes mellitus, chronic renal insufficiency, and hyperuricemia (González-Lara et al. 2014; Hari Kumar et al. 2010; Kurban et al. 2008; Robles-Mendez et al. 2015). More rarely associated diseases are hypothyroidism, Hodgkin's lymphoma, hepatocellular carcinoma, thyroid cancers, and dermatomyositis (Wagner and Sachse 2013).

Our patient presented with advanced liver disease, jaundice, and severe pruritus, but no chronic renal insufficiency or hyperuricemia. She had mild diabetes mellitus (HbA1c 6.1%, metformin mono-therapy) and no renal disease. In the literature, the majority of ARPD patients suffer from diabetes mellitus associated with chronic renal disease and haemodialysis. In addition, our patient has had diabetes for many years before ARPD occurrence. Importantly, the condition of her skin improved finally under PBC treatment, suggesting a correlation between skin and liver disease. It can be concluded that ARPD was not linked to diabetes in our patient.

PBC Linked to Skin Disorders: Review of the Literature

We performed a literature search on PBC associated with skin conditions. A PubMed search was done. Papers in all languages were considered. Systemic autoimmune diseases with skin manifestations, such as systemic lupus erythematosus, systemic sclerosis (SS), SSY, dermatomyositis, multiple autoimmune syndromes or rare syndromes, such as Reynolds's syndrome (PBC associated with SS) and PACK (PBC, anti-centromere antibody, CREST syndrome, and

keratoconjunctivitis sicca) syndrome, were not considered as being skin diseases (Cabane 2010; Powell et al. 1987).

The association of PBC with some dermatological manifestations is known since a long time. In a prospective evaluation study from Greece of 49 PBC patients compared with a control group, a statistically significant higher presence of dermatological manifestations, such as pruritus, xerosis, dermographismus, pigmentary changes, neoplastic lesions, and skin fungal infections, was observed (Koulentaki et al. 2006). The first case of prurigo secondary to scratching because of itching associated with PBC was reported in 1959 (Sallet et al. 1959). Ten years earlier, the relationship between serum lipids and xanthomata was described for the first time: this association is strong enough to justify that PBC was initially named "xanthomatous biliary cirrhosis" (Ahrens and Kunkel 1949; MacMahon 1948). In the subsequent years, other publications on the topic of xanthomatoses followed, particularly xanthelasmas (Bevans and Batchelor 1950; Lever and MacLean 1950) and, later, xanthoma striatum palmare (Hsu et al. 2005; Macías-Rodríguez and Torre-Delgadillo 2006).

Many papers analysing extrahepatic autoimmune disease in PBC patients do not consider skin diseases (Corpechot et al. 2010; Muratori et al. 2015; Parikh-Patel et al. 2001). This could be due to the fact that autoimmune skin diseases are relatively rare extrahepatic autoimmune diseases in PBC or are considered to be mild and not relevant. However, being pruritus a frequent symptom in many liver diseases, we cannot exclude imprecise skin evaluation by non-dermatologists with subsequent underdiagnosis of a specific skin disease.

The present literature review has highlighted some rare dermatoses associated with PBC reported in one or two cases, such as panniculitis (Herr et al. 1996), cutaneous amyloidosis (Hsu et al. 2005; Lever and MacLean 1950), scleredema adultorum Buschke (Goss et al. 1984), acanthosis nigricans (Pham et al. 1996), or prurigo pigmentosa (Togawa et al. 2004) (Table 1). Since these are all case reports, it is not possible to establish if these rare dermatoses are more frequent in PBC patients than in the general population.

Instead, there is a group of skin diseases which are reported more frequently, such as autoimmune blisters diseases, vitiligo, lichen planus, lichen sclerosus et atrophicus, psoriasis, cutaneous vasculitis, and neutrophilic and granulomatous skin diseases (Table 1).

Among autoimmune bullous diseases, the most frequently reported are bullous pemphigoid (Grange et al. 1983; Guerra-Uribe and González-Huezo 2016; Hamilton and McKenzie 1978; Marcet et al. 2002; Singhal and Scharschmidt 1985) followed by dermatitis herpetiformis (Gabrielsen and Hoel 1985; Walton and Walton 1987), which is virtually always linked to celiac disease. Only one case of a disease belonging to the pemphigus group has been published in association with PBC. This patient had an undefined superficial pemphigus appearing after treatment with D-penicillamine, a drug known to induce this type of pemphigus (Gibson and Dicken 1985), so that it can be argued that there is no link between PBC and undefined superficial pemphigus in this case (Table 1). Again, all of these papers are case reports.

Lichen planus is the dermatosis that has been most frequently reported in association with PBC (Table 1). However, a controlled study of 577 patients with lichen planus pointed to a significant association with chronic liver diseases, but no case was associated with PBC (Rebora et al. 1992). No studies reporting the prevalence of lichen planus in large series of PBC patients are available.

An Italian study of 361 cases (Floreani et al. 2015) reported a 5.0% frequency of skin disorders linked to PBC, including vitiligo and lichen planus, but did not differentiate among the single skin disorders. In a monocentric French cohort of 222 PBC patients (Corpechot et al. 2010), PBC-associated inflammatory or autoimmune skin conditions were psoriasis (6%) and vitiligo (2%). A cohort of 71 patients with overlap PBC/AIH from Turkey, Italy, France, and Sweden was analysed for associated extrahepatic autoimmune diseases, including skin conditions (Efe et al. 2012). Psoriasis was found in three patients (4.2%), and vitiligo in two patients (2.8%). Finally, a single center study from Italy including 119 PBC patients did not found any case with associated skin conditions (Muratori et al. 2015).

The prevalence of psoriasis varies according to ethnic or environmental factors (insolation). In the European population, it increases from about 2% in Central Europe up to 5% in Norway. The frequency rate reported in the study from France (Corpechot et al. 2010) is slightly higher than frequency in the general population, whilst the international study (Efe et al. 2012) includes countries with high and low psoriasis prevalence, the median prevalence is not higher than the general population. The absence of patients affected by psoriasis in the Italian cohort can be due to the small number of analysed patients, but suggests that psoriasis is not more frequent in PBC patients than in the general population.

The vitiligo rate is about 1% of the world population. The reported rate in the above-mentioned studies is 2%, but the number of analysed subjects is too small to allow us to conclude about a significant difference.

The association between PBC and vasculitis or neutrophilic dermatoses is fairly anecdotic (Table 1).

The simultaneous presence of cutaneous granulomatous diseases, particularly sarcoidosis, and PBC may lead us to speculate on a possible common pathway for the formation of granulomas. One explanation for this dilemma could be that sarcoidosis and PBC may share similar defects in

Table 1 Cutaneous autoimmune, inflammatory, neutrophilic, or granulomatous diseases associated with PBC

Skin condition	Number of cases	Year	Country	References
Autoimmune bullous diseases				
Bullous pemphigoid	1	1978	UK	Hamilton and McKenzie (1978)
	1	1983	France	Grange et al. (1983)
	1	1985	USA	Singhal and Scharschmidt (1985)
	1	2002	France	Marcet et al. (2002)
	1	2016	Mexico	Guerra-Uribe and González-Huezo (2016)
Dermatitis herpetiformis	1	1985	Norway	Gabrielsen and Hoel (1985)
	1	1987	UK	Walton and Walton (1987)
Pemphigus superficialis (erythematosus)	1	1985	USA	Gibson and Dicken (1985)
Lichen planus	5	1982	UK	Graham-Brown et al. (1982)
	1	1982	USA	Powell et al. (1983)
	1	1994	USA	Gart and Camisa (1994)
	1	1990	UK	Mc Donagh et al. (1990)
	24	1984	Sweden	Mobacken et al. (1984)
	1	1984	UK	Epstein (1984)
	1	1986	Sweden	Weismann et al. (1986)
	1	1989	Sweden	Strauss et al. (1989)
	1	1989	Sweden	Sowden et al. (1989)
	1	1990	Italy	Liberal et al. (2016)
	1	1994	USA	Gart and Camisa (1994)
	1	1995	Spain	Oleaga et al. (1995)
	1	2000	Taiwan	Chu et al. (2000)
	3	2003	Germany	Friedrich et al. (2003)
	1	2014	Japan	Nagao and Sata (2014)
Vitiligo	1	1984	Israel	Enat and Gilhar (1984)
	1	1986	Italy	Zauli et al. (1986)
	1	2002	Puerto	Seiglie et al. (2014)
	1	2014	Rico	Corpechot et al. (2010)
	4	2010	France	Efe et al. (2012)
	2	2012	France, Italy, Sweden, Turkey	
Lichen sclerosus et atrophicus	1	1986	UK	Graham-Brown and Sarkany (1986)
	1	1986	UK	Natarajan and Green (1986)
	1	1986	UK	Meyrick Thomas et al. (1986)
	1	1985	Northern Ireland	Lavery et al. (1985)
Morphea	1	1986	UK	Natarajan and Green (1986)
	1	1986	Japan	Suyama et al. (1986)
	1	1992	UK	Wong and Holt (1992)
	1	2000	UK	Reed et al. (2000)
	1	2006	Spain	González-López et al. (2006)
Psoriasis	1	1993	Japan	Okaniwa et al. (1993)
	13	2010	France	Corpechot et al. (2010)
	3	2012	France, Italy, Sweden, Turkey	Efe et al. (2012)
	1	2006	Japan	Iwadate et al. (2006)
Vasculitis				
Purpura Henoch-Schönlein	2	2007	Greece	Gatselis et al. (2007)
Pustular vasculitis	1	2006	UK	Koulaouzidis et al. (2006)
Cutaneous polyarteritis nodosa	1	2000	Japan	Dohmen et al. (2000)
Leukocytoclastic vasculitis	3	1985	Denmark	Diederichsen et al. (1985)
Circulating immune complexes vasculitis	1	1984	USA	Terkeltaub et al. (1984)

Table 1 (continued)

Skin condition	Number of cases	Year	Country	References
Churg-Strauss vasculitis	1	1982	USA	Conn et al. (1982)
Temporal arteritis	1	1988	France	Gagnerie et al. (1988)
Takayasu's arteritis	1	2004	Germany	Feist et al. (2004)
Behçet disease	1	1992	UK	Jankowski et al. (1992)
	1	2006	Japan	Iwadate et al. (2006)
Neutrophilic dermatoses				
Sweet dermatosis	1	2008	USA	Owen et al. (2008)
	1	2014	USA	Kaminska et al. (2014)
Pyoderma gangrenosum	1	1983	USA	Maturi et al. (1983)
Cutaneous sarcoidosis and other non-infectious granulomas				
Cutaneous granulomas after liver transplantation	1	2000	Israel	Armali et al. (2000)
Cutaneous sarcoidosis	1	1994	Greece	Asvesti et al. (1994)
	1	1987	USA	Keeffe (1987)
	1	1992	USA	Harrington and Fitzpatrick (1992)
	1	1988	USA	Sherman et al. (1988)
	2	2008	USA	Kishor et al. (2008)
Generalized granuloma annulare	1	1990	Japan	Koizumi et al. (1990)
Cutaneous granulomata	1	1977	UK	Byrne et al. (1977)
	1	1994	New Zealand	Jardine et al. (1994)
Sarcoidosis	1	1997	UK	Hughes and McGavin (1997)
	1	2010	Japan	Sakamoto et al. (2010)
Panniculitis	1	1996	Germany	Herr et al. (1996)
Cutaneous amyloidosis	1 1	2015	Mexico	González-Moreno et al. (2015), Tafarel et al. (2007)
		2007	Brazil	Tafarel et al. (2007)
Sceroderma adultorum Buschke	1	1984	Germany	Goss et al. (1984)
Acanthosis nigricans	1	1996	Australia	Pham et al. (1996)
Prurigo pigmentosa	1	2004	Japan	Togawa et al. (2004)

cell-mediated immunity. In both diseases, granulomas show an accumulation of CD4 T cells within the center of the granuloma. CD8 T cells are present in the periphery of sarcoidal granulomas and near bile ducts in PBC (Kishor et al. 2008). However, the reported number of cases with regard to this association is just over ten (Table 1). In our opinion, this number is too low, not allowing us to speculate about a common pathogenetic pathway.

Conclusion

We report the case of a 60-year-old woman being diagnosed with ARPD, SSY, and PBC. Dermatologists and hepatologists together managed this rare disease combination with an interdisciplinary approach. Combined liver and skin treatment improved both her skin disorder and her cholestasis and liver function. At last follow-up, she had normal liver function tests, healing of cutaneous lesions (Fig. 4), and complete resolution of pruritus. The documented recovery is in line with the previous reports about simultaneous improvement of skin and liver disease (Kahana et al. 1985; Mahajan et al. 2004). This observation suggests that the two conditions may be causatively linked. Therefore, a close collaboration between dermatologists and hepatologists seems to be essential for the optimal management of patients with coexisting skin and autoimmune liver disorders.

As documented by the current literature review, the vast majority of the papers dealing with skin disorders associated with PBC are case reports. Only few studies on large PBC patient's groups are available, and this makes difficult to know the real prevalence of skin diseases in PBC patients. The available studies found only a slightly higher prevalence of psoriasis and vitiligo than in the general population, questioning the general assumption

about lichen planus, vitiligo, and psoriasis being more prevalent in PBC patients. More data are needed from large PBC cohorts about specific skin disorders associated with it.

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