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CASE REPORT

Severe and Prolonged Liver Damage in Pityriasis Rubra Pilaris Treated with acitretin: a Case Report

Katrin Rak[1] · Henning Hamm[1] · Andreas Kerstan[1] · Annette Kolb-Mäurer[1] · Matthias Goebeler[1]

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Abstract

Acitretin is a systemic retinoid that is used in dermatology for treatment of various inflammatory and especially hyperkeratotic diseases. Elevation of liver enzymes may occur occasionally but normally resolves spontaneously, at the latest after termination of acitretin. However, it can very rarely develop into a life-threatening adverse event including drug-induced liver injury (DILI). A 45-year-old man with classical pityriasis rubra pilaris, a frequently severe, inflammatory skin disease, was started on acitretin. After a seemingly harmless elevation of transaminases, a few weeks after initiation of acitretin, the patient experienced a dramatic course of liver injury with hepatic jaundice though acitretin was stopped immediately. Eventually, laboratory values recovered upon high-dose oral prednisolone therapy. Prescribing physicians should keep in mind that acitretin might induce severe liver injury. Even after termination of acitretin laboratory values should be monitored for a while in order to recognize symptomless but harmful drug-induced liver injury in time.

Keywords Acitretin · Pityriasis rubra pilaris · Drug-induced liver injury (DILI) · Adverse event

Introduction

Acitretin, a systemic retinoid receptor agonist, is administered for a broad variety of inflammatory and hyperkeratotic diseases. Its application has to be considered carefully with special attention to its harmful teratogenicity. Common side effects include dry skin and mucous membranes, dyslipoproteinemia and hair loss. Another frequent, but mostly harmless and reversible adverse effect is the elevation of liver enzymes [1].

Here, we report the case of a 45-year-old man with pityriasis rubra pilaris (PRP), who developed severe drug-induced liver injury (DILI) upon administration of acitretin leading to temporary liver dysfunction although acitretin was stopped. PRP is a rare papulosquamous, inflammatory skin disease that is characterized by a broad spectrum of presentations ranging from mild manifestations confined to extremities to severe disease developing into erythroderma. Its typical feature are follicular keratotic papules with reddish-orange hue and in more generalized subtypes islands of sparing (so called "nappes claires"). The pathogenesis of PRP is poorly understood, and treatment options are limited. Retinoids are considered first-choice systemic treatment [2].

Case Presentation

A 45-year-old man with an otherwise unremarkable medical history was referred to our department presenting with the typical clinical picture of classical adult PRP with confluent follicular, hyperkeratotic, reddish-orange papules and plaques that were intervened by nappes claires on his extremities and his trunk and with keratoderma on his palms and soles (Fig. 1). Two weeks before the rash had begun with a rough reddish plaque on the forehead. Despite of topical treatment with corticosteroids and the initiation of oral prednisolone 50 mg once daily skin manifestations continued to spread in a cephalocaudal direction ending up in suberythroderma. Histopathology substantiated the diagnosis of PRP. After admission, acitretin was initiated in a dose of 50 mg (0.66 mg/kg body weight) once daily, and prednisolone was terminated. Topical treatment with

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✉ Katrin Rak
rak_k1@ukw.de

[1] Department of Dermatology, Venereology and Allergology, University Hospital Würzburg, D-97080 Würzburg, Germany

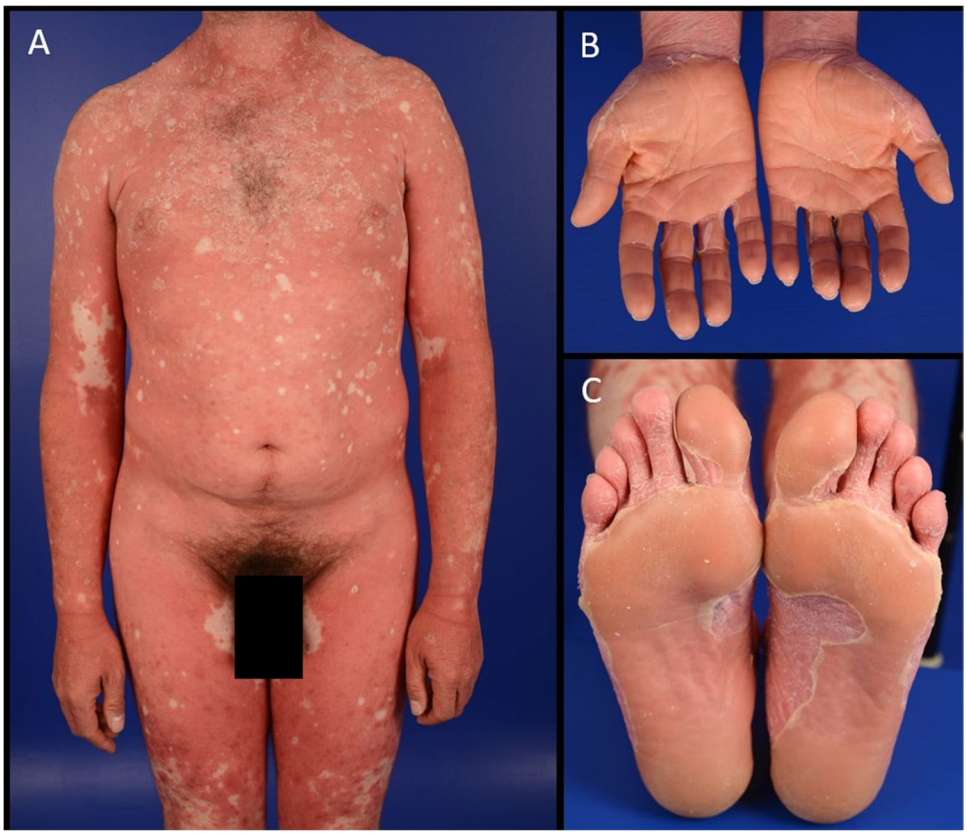

Fig. 1 Clinical presentation before treatment with acitretin. **A** Confluent follicular, hyperkeratotic, reddish-orange papules and plaques intervened by islands of sparing ("nappes claires") on trunk and extremities. **B**, **C** Palmar and plantar keratoderma. The figure was created with Adobe Photoshop

potent corticosteroids was applied twice daily. Nine days later, the patient was discharged in good general condition and with inconspicuous routine laboratory values. At his first appointment in our outpatient clinic 2 weeks later, the skin had improved significantly showing less infiltration and desquamation. Except for dry lips and a certain degree of hair loss acitretin was well tolerated in the first months of treatment. However, 3 months after initiation of acitretin, a substantial elevation of liver enzymes (alanine aminotransferase (ALT) > 15 × upper limit of normal (ULN), aspartate aminotransaminase (AST) > 7 × ULN) and gamma-glutamyltransferase (GGT, > 2.5 × ULN) was noted accompanied by generalized itch (Fig. 2). Despite immediate termination of acitretin therapy, the transaminases (ALT > 28 × ULN, AST > 13 × ULN) and GGT (> 3 × ULN) continued to increase. Simultaneously, hyperbilirubinemia and a scleral icterus developed indicating a cholestatic disorder. The patient was referred to the department of internal medicine where the presumptive diagnosis of acute drug-induced liver injury (DILI) was histopathologically confirmed by a liver biopsy that showed centrilobular (zone 3) necroses and resorption but no signs of autoimmunological, viral, or hereditary causes. Complementary serological tests ruled out viral infections (hepatitis A, B, C, and E, cytomegalovirus) and syphilis. Interestingly, elevated antinuclear antibodies (ANA) (titer 1:640) and a human leucocyte antigen

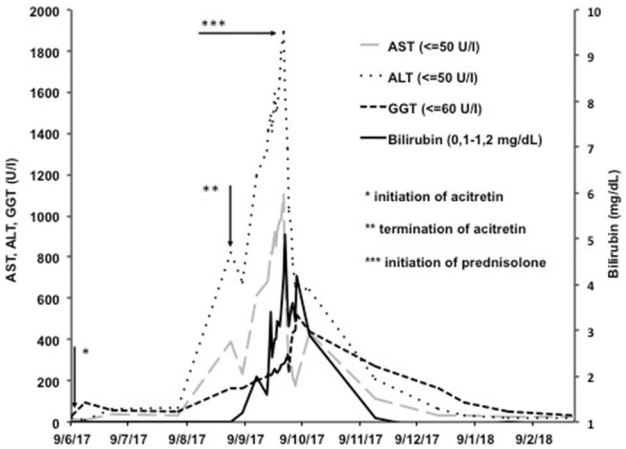

Fig. 2 Monitoring of liver enzymes and bilirubin after start (*) and end (**) of treatment with acitretin. A time course of 8 months is depicted. The Figure was created with Microsoft Excel and Powerpoint

(HLA) constellation indicating susceptibility for autoimmune hepatitis (HLAB08 and HLADRB1*03) were detected [3]. Even four weeks after treatment termination hepatocellular and cholestatic laboratory values (ALT > 35 × ULN U/I, AST > 20 × ULN, GGT > 9 × ULN, bilirubin 1,2 x ULN) kept on rising (Fig. 2). A marked liver dysfunction

was noticed by an increased international normalized ratio (INR) of 1.33 and a decrease of cholinesterase. All led to the initiation of oral prednisolone in a daily dose of 70 mg. The systemic therapy resulted in rapid improvement of laboratory parameters. Two weeks later, the patient was dismissed with stabilizing liver and cholestatic values (ALT > 3 ULN, AST > 15 × ULN, GGT > 7 × ULN, bilirubin 3.6 mg/dL, normalized INR) (Fig. 2). However, due to an undulating course of liver enzymes, prednisolone had to be continued at low levels for a period of 9 months in total. In the meantime, the patient was offered the induction of secukinumab, an IL-17-antagonist, to treat his skin manifestations. Biologicals, especially IL-17-antagonists, have been described to be a promising and safe off-label treatment option for PRP [4]. As the patient had experienced severe hepatotoxic side effect, he expressly dispensed with a new therapy. Eventually, skin lesions almost resolved without further systemic therapy. The patient had no further discomfort regarding his DILI and PRP until today.

Discussion

PRP is a rare inflammatory skin disease. While medical guidelines are yet not available, oral retinoids used in higher doses are widely considered a first-line treatment for PRP. Acitretin, the preferred retinoid, is given in doses of 0.5–0.75 mg/kg body weight daily with the principal meal [2, 5–7]. Even in the era of biologicals and small molecules, acitretin is regarded as a promising and effective medication not only for PRP.

By activating nuclear retinoid receptors, it is involved in the regulation of cell proliferation and differentiation (keratinisation). Furthermore, it has anti-inflammatory effects. Acitretin is the major metabolite of the formerly used etretinate, which it has replaced completely in clinical practice because of better pharmacokinetics. Its main advantages are a shorter half-life and minor accumulation in adipose tissue resulting in a more favourable side effect profile. Of note, acitretin can undergo reverse metabolism to etretinate, in particular in combination with consumption of alcohol. After its metabolisation, acitretin is eliminated in the bile or through the kidneys [8].

However, mucocutaneous dryness, lipid dysfunction, or hair loss often leads to premature termination, and its use may further be limited by potentially severe side effects. Adverse effects to the liver are the reason for regular laboratory tests especially in the beginning of therapy. Reported prevalences of transaminase elevation during acitretin treatment range from less than 1 to up to 16% [9]. Marked elevations (> 3 × ULN) are estimated to occur in 1–5% of acitretin-treated patients. In most of the cases, abnormalities resolve spontaneously even with sustained use or elsewise after discontinuation of acitretin and are not accompanied by other symptoms. DILI developing upon systemic retinoid administration is a rare event and estimated to occur in 0.1–0.5% [10]. Several studies conducted with patients suffering from different psoriasis subtypes confirmed that severe liver injury is a very rare side effect of acitretin. In 1990, a prospective, open-label trial demonstrated that even long-term therapy with acitretin did not cause clinically significant biopsy-proven hepatotoxicity [11]. Liver biopsies performed on 128 patients before and 2 years after systemic treatment with acitretin (25–75 mg/day) did neither indicate a correlation between elevation of transaminases nor the cumulative dose with the degree of liver injury. A retrospective study published in 2004 confirmed that significant elevation of transaminases is very unlikely to appear under long-term low-dose acitretin [12]. In 2019, another observational study attested that severe hepatic side effects under low-dose acitretin are very uncommon. None of 104 patients who were treated with acitretin in a mean dose of 20 mg daily over a mean time of 3.2 years developed severe liver side effects [13].

However, few cases of DILI under acitretin have been described [14–18]. In our case, unlike other observations, discontinuation of acitretin did not lead to an improvement of complications. Instead, liver enzymes continued to rise to a very high extent and were accompanied by scleral icterus, nausea, itching, weakness, and poor concentration and eventually ending up in a liver dysfunction. Especially, the detection of elevated ANAs and a typical HLA-constellation opened the discussion of an autoimmunological component having aggravated the progression and long duration of the acitretin-induced liver injury. Cofactors (e.g., alcohol consumption) might have contributed to acitretin having been sequestrated in fatty storage sites leading to systemic distribution and liver damage despite discontinuation. However, our patient denied alcohol consumption. Otherwise, due to its half-life of 50 to 60 hs, acitretin must have been eliminated a few days after termination.

The actual reason for the long duration of liver injury with transaminases staying at a high level remains unclear and the limitation of the reported case.

Conclusions

The presented case emphasizes the harmful potential of a well-known, but underestimated side effect of a frequently used drug. Prescribing physicians should not fear to initiate acitretin but always bear in mind its potential hepatotoxic adverse effects even after termination.

Authors' Contribution All authors were involved in medical care of the patient and critically revised the manuscript to bring it into its final version. All authors gave final approval of the version to be published.

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Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Written consent for publication was given by the patient.

Conflict of Interest The authors declare no competing interests.

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