Red Skin Syndrome

16

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Abstract

Red skin syndrome (RSS) is a condition that can develop after stopping long-term continuous use of topical steroids. In RSS, erythema or exudative erythema extends from the original location of the rash where topical steroids had been applied to sites where steroids were never used. The disorder may take weeks to several years to resolve and some patients experience repeated seasonal exacerbation long term.

Keywords

Topical steroid addiction (TSA) • Topical steroid withdrawal (TSW) • 11-Beta-HSD2

Learning Points

1. RSS cases have often been misdiagnosed as a flare of the underlying dermatological disorder.
2. RSS can be diagnosed through observation of the rash over time.
3. There is a possibility that the long-term continuous use of topical steroids affects the cortisol production by keratinocytes, thereby causing RSS.

The name RSS was coined by Dr. Rapaport in 2006 [1] to describe a previously unrecognised condition. RSS goes by many names in the literature, and even Rapaport has also used alternative terms such as red scrotum syndrome [2] and red burning skin syndrome [3]. The International Topical Steroid Addiction Network (ITSAN), a patient-led group working to spread awareness about RSS mostly through their website, uses the terms topical steroid addiction (TSA) and topical steroid withdrawal (TSW) in addition to RSS. In Japan, RSS was reported by Dr. Enomoto in 1991 as 'steroid withdrawal syndrome by topical corticosteroid' [4]. The condition has also been called 'steroid dermopathy' or simply 'rebound'.

RSS presents in different ways with a range of diverse clinical features. It occurs after the

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cessation of chronic continuous use of topical steroids. Symptoms are more severe than the original skin condition (i.e. before treatment with topical steroids). The skin symptoms often appear similar to an exacerbation of the original skin condition that triggered the use of topical steroids in the first place. Therefore, RSS cases have often been misdiagnosed as a flare of the underlying dermatological disorder. RSS can only be diagnosed through observation of the rash over time. However, several features are characteristic, such as the distribution of the rash and its progression.

The first part of this chapter will describe clinical manifestations seen in RSS cases. The second will discuss causes of RSS and the final section will outline treatment of RSS.

16.1 Clinical Manifestation of RSS

RSS often develops in patients with a history of atopic dermatitis (AD). When a patient with AD ceases chronic continuous use of topical steroids, several scenarios may follow [5], including:

1. Simple AD recurrence.
2. Possible RSS. This is difficult to distinguish from recurrent AD symptoms (see Fig. 16.1 for an example).
3. Definite RSS.

Looking at the rash in the series of photographs 1, 2, 3 and 4 in Fig. 16.1, the dermatological diagnosis would clearly be AD. There is no obvious reason to consider the diagnosis of RSS. Photo 1 shows the patient shortly before discontinuing topical steroids where the rash was poorly controlled. Photo 2 was taken 2 months after ceasing topical steroids; photo 3, 7 months after cessation; and photo 4, 12 months after cessation. The patient did not make any lifestyle or environmental changes in those 12 months—all he did was stop the use of topical steroids. If his diagnosis was contact dermatitis secondary to the topical steroids used, then recovery should have been swift. His skin would not have gotten worse as it did—the severity of his symptoms actually peaked during the 2nd month before improving over the next few months. So, if you consider the rash at just one point in time, the diagnosis would almost certainly be AD. However, taking into account the history of topical steroid use and then cessation and the subsequent progression of the rash, the diagnosis of RSS is obvious.

It is easy to make a diagnosis of RSS when the patient's symptoms are severe, as in the case shown in Fig. 16.2. Photograph 1 was taken just before the patient discontinued topical steroids. Here, the patient's skin condition appears too severe to be a typical case of AD. In photo 2, taken 2 months after cessation of topical steroids,

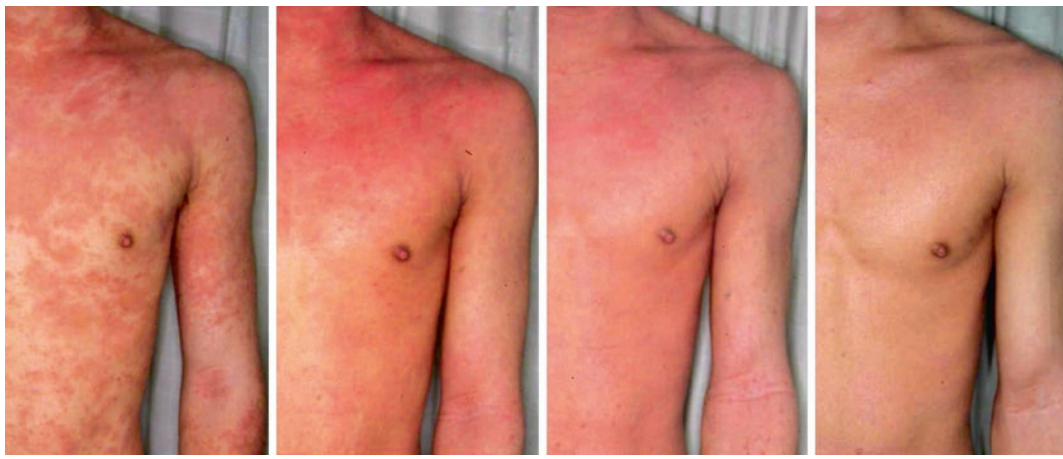

Fig. 16.1 Prior to discontinuation/2 months later/7 months later/12 months later

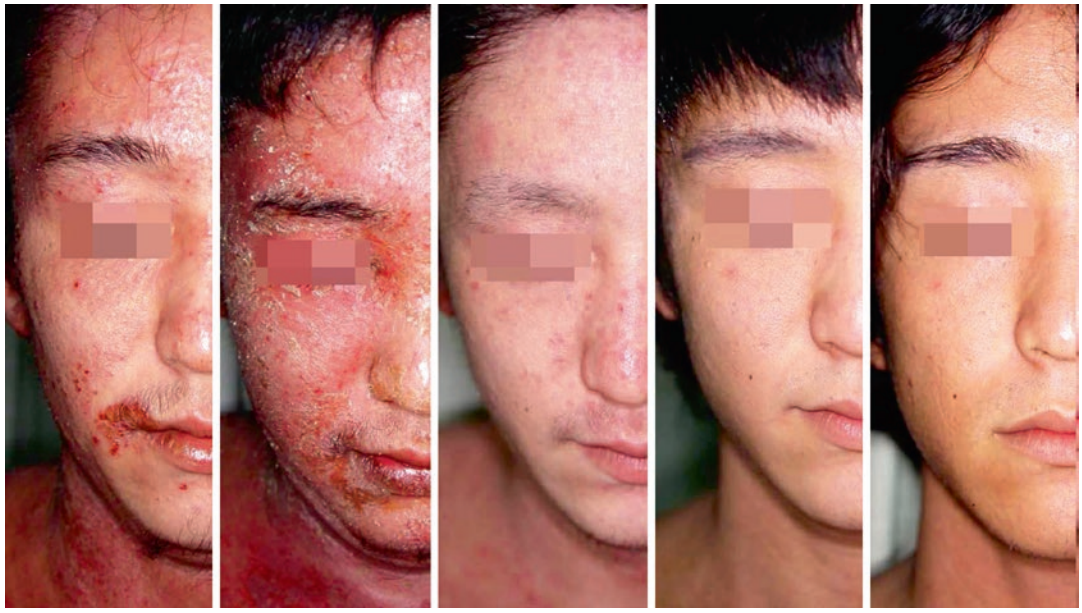

Fig. 16.2 Prior to discontinuation/2 weeks later/3 months later/7 months later/13 months later

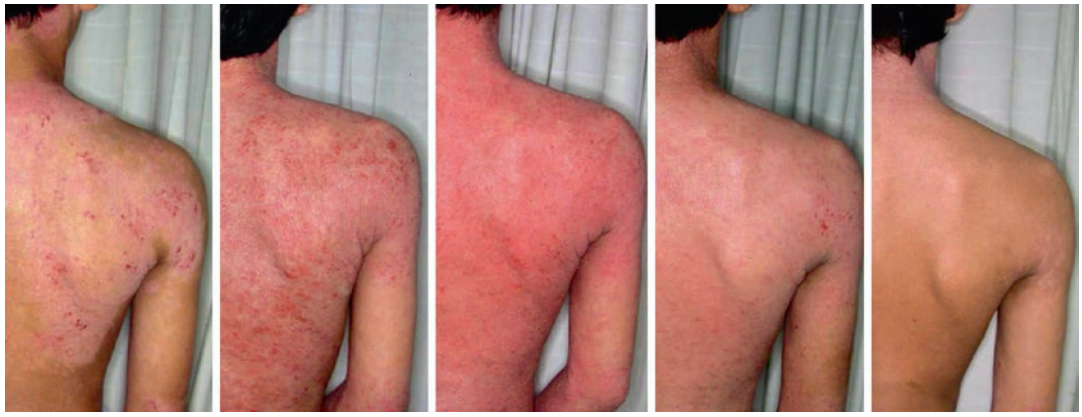

Fig. 16.3 Prior to discontinuation/3 months later/7 months later/11 months later/19 months later

we see exudative erythema, incrustation, exfoliation, pigmentation and scars secondary to scratching. The patient developed a fever of around 40° which lasted 7–10 days and was thus suspected of having adrenal insufficiency. However, his blood cortisol levels were actually raised (not reduced).

In some cases RSS progresses slowly after discontinuation of topical steroids. In these cases both the doctor and patient may become disheartened and doubtful whether management is appropriate. In Fig. 16.3 we see a case where symptoms peaked 7 months after ceasing topical steroids before gradually resolving.

After ceasing topical steroids, a patient with RSS will develop extremely sensitive skin, and dermatitis will appear following exposure to even slight irritation. False positives are common in patch tests done around this time. Temporary exacerbations may result from seasonal changes such as changes in temperature and/or humidity or shedding of hair by pets. Unexpected flares can occur, for example, when a patient moves to a new location. Patients can thus experience a second or third rebound.

Therefore to determine whether a patient is heading towards recovery, the doctor needs to observe the patient for at least 12 months, ideally comparing skin status throughout the seasons over several years. For example, the patient in Fig. 16.3 can be assured of their improvement by comparing photos taken at 7 and 19 months after cessation of topical steroids.

16.2 Causes of RSS

Rapaport focussed on the vasodilation action of nitric oxide (NO) and suggested NO was a cause of RSS [6]. Cork proposed a theory that topical steroids increase protease, which breaks down corneodesmosome, which is in turn known to bind corneocytes to each other, and this is what breaks down the epidermal barrier leading to rebound symptoms [7].

In recent years it has been found that keratinocytes produce cortisol to autoregulate epidermal thickness and differentiation by paracrine and autocrine mechanisms [8]. The author believes that the long-term continuous use of topical steroids affects the cortisol production by keratinocytes, thereby causing RSS [9, 10].

Figure 16.4 shows the epidermal changes seen on the inside forearm of a healthy individual who had applied 0.05% clobetasol propionate twice daily to the area for 2 weeks before stopping. The images shown are of the skin before topical steroid use, day 2 of use, day 15 (i.e. 1 day after ceasing topical steroids) and day 30 (i.e. 16 days after stopping the topical steroid). Immunostaining for anti-PCNA antibodies, anti-cortisol antibodies, anti-11-beta-HSD1 antibodies and anti-11-beta-HSD2 antibodies is demonstrated. Atrophy to epidermis is evident on day 15, and on day 30 this atrophy was seen to be resolving. The intracytoplasmic cortisol in the keratinocytes peaked on day 15, showing the topical steroid use caused an increase in the cortisol production by the epidermis. This response has already been demonstrated in dermal fibroblasts [11]. It appears that the concentration of cortisol in the skin varies almost immediately in response to blood levels of cortisol (which are determined by the adrenal cortex).

Intracytoplasmic cortisol and 11-beta-HSD2 both increase in keratinocytes. 11-Beta-HSD1 is an enzyme that converts cortisone, an inactive steroid, into cortisol, whilst 11-beta-HSD2 converts cortisol into cortisone. Therefore, increased levels of 11-beta-HSD2 indicate cortisol within the keratinocytes is being inactivated.

Figure 16.5 demonstrates a patient's epidermis with immunostaining during RSS and during recovery 2 years later.

The amount of 11-beta-HSD2 near the basal level is increased during RSS. In the recovered epidermis, 11-beta-HSD2 levels had reduced. The epidermal thickness has normalised, as has the granular layer, and the parakeratosis has disappeared. The evidence from this case suggests increased 11-beta-HSD2 in the epidermal basal layer is a cause of RSS. This means cortisol is inactivated to cortisone in the keratinocytes leading to increased proliferation of basal cells and immature keratinisation. This is explained in the diagram in Fig. 16.6.

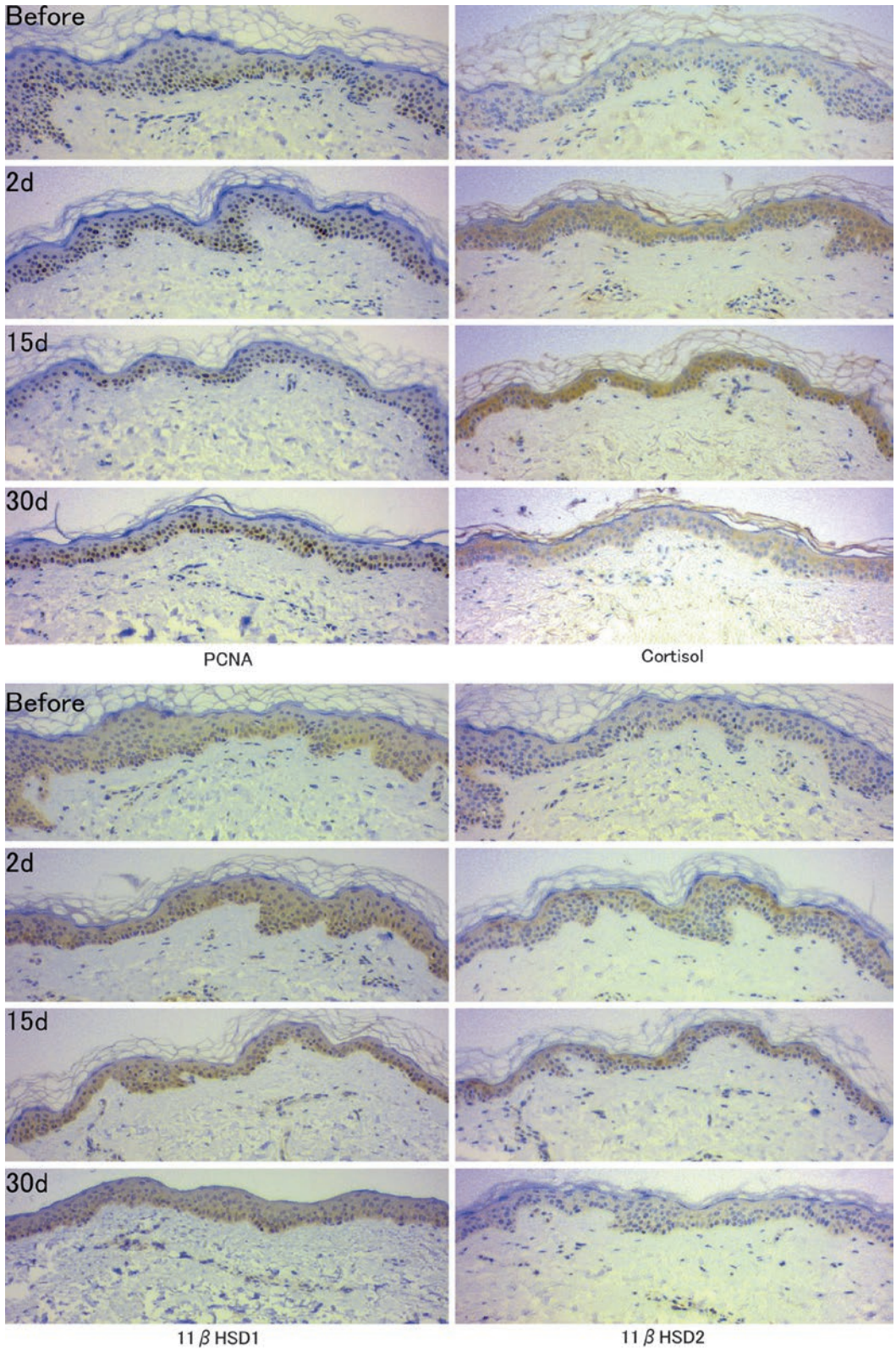

Fig. 16.4 The epidermal changes seen on the inside forearm of a healthy individual who had applied 0.05% clobetasol propionate twice daily to the area for 2 weeks before stopping

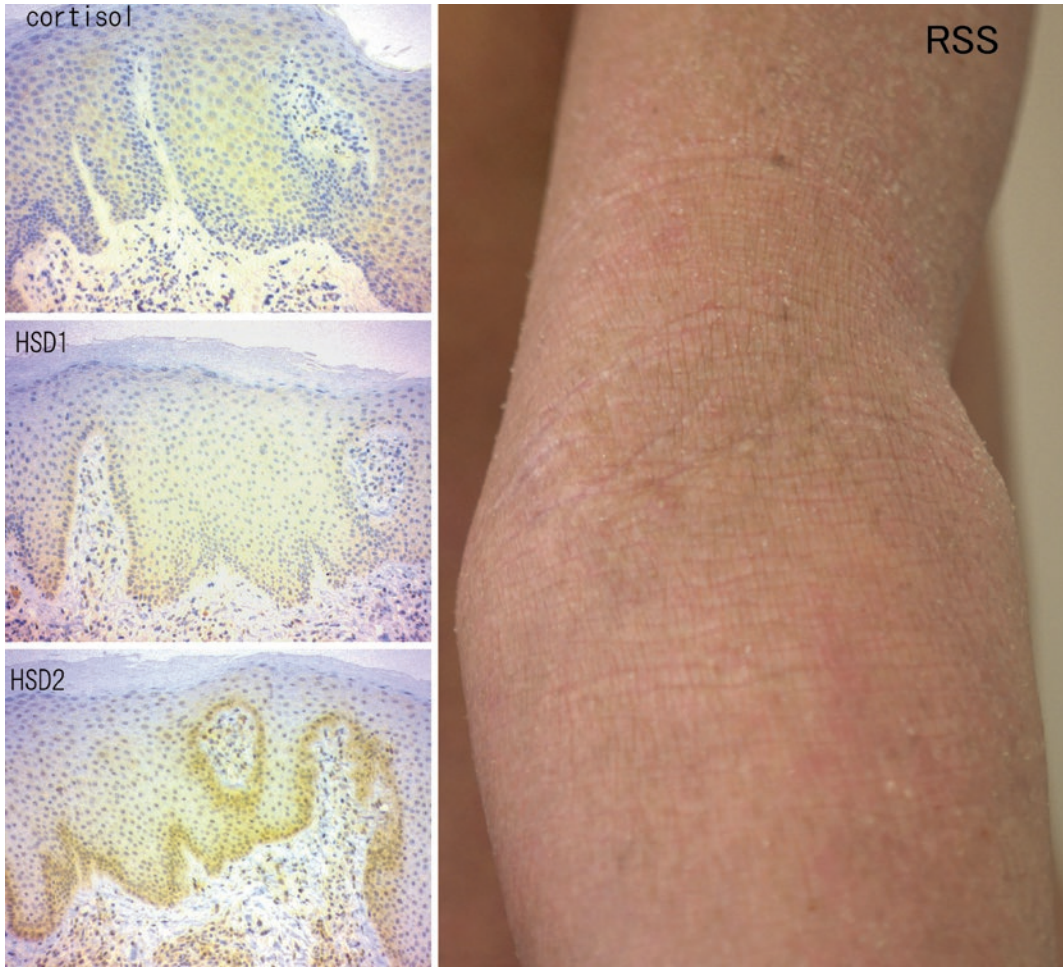

Fig. 16.5 A patient's epidermis with immunostaining during RSS and during recovery 2 years later

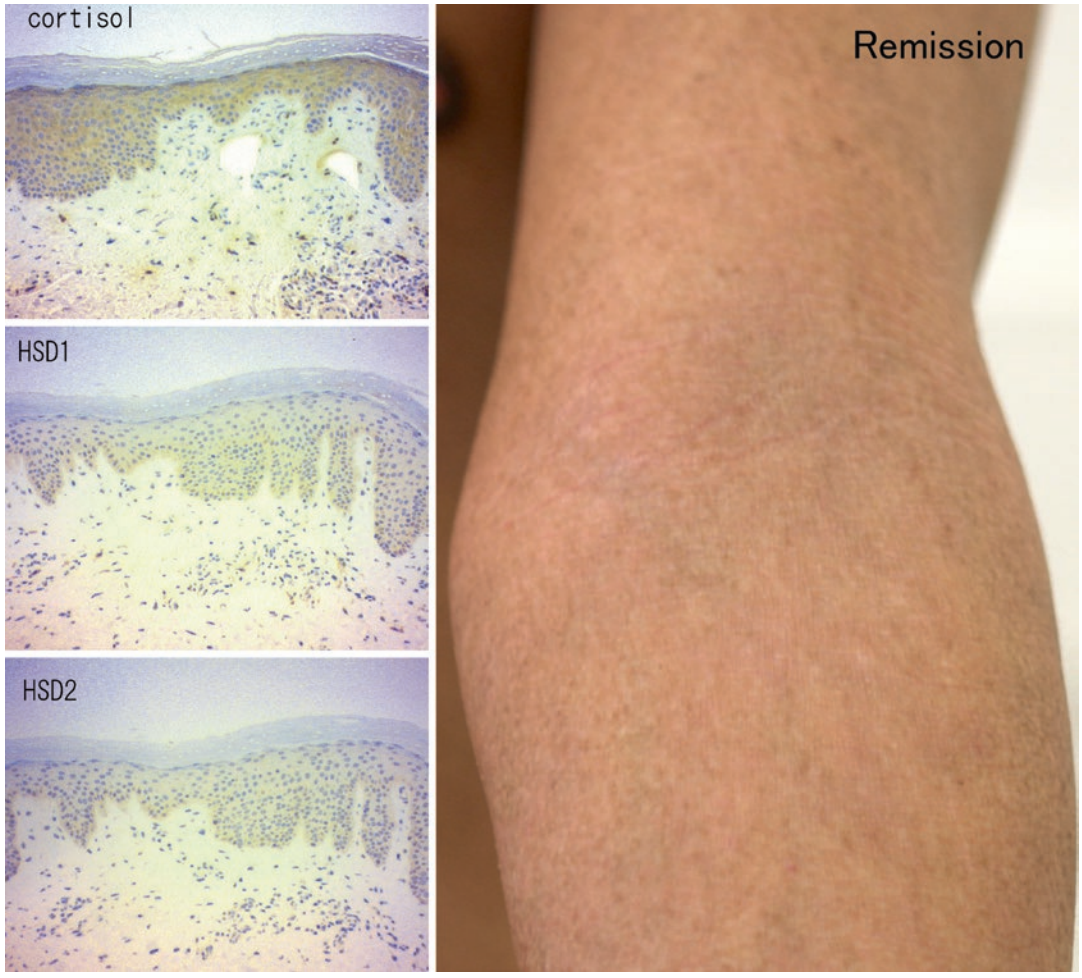

Fig. 16.5 (continued)

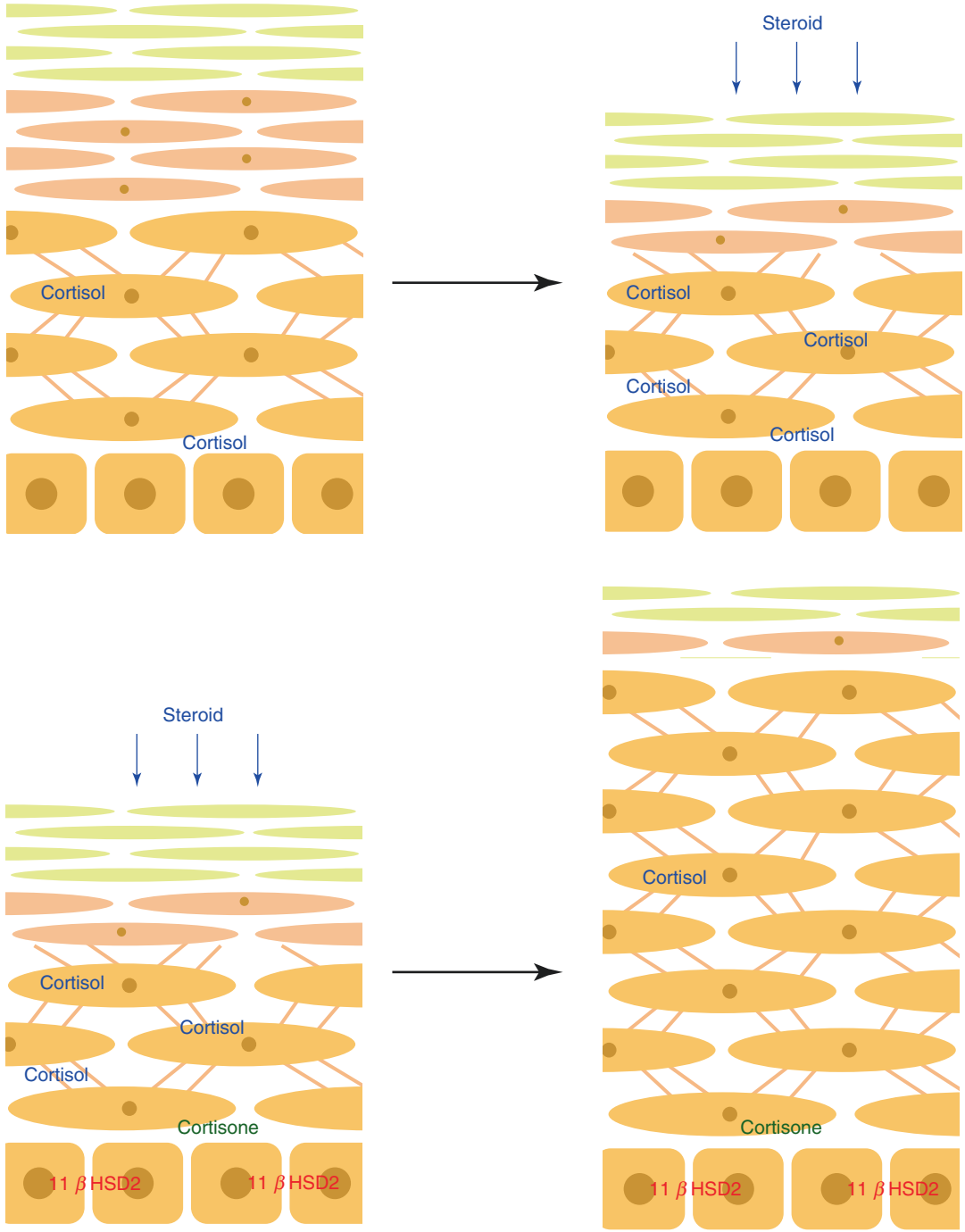

Fig. 16.6 The first picture shows normal epidermis before application of topical steroids. The second shows increased cortisol levels and a thinner epidermis as a result of topical steroid application. The third picture shows the epidermis's progression to topical steroid addiction with increased levels of 11-beta-HSD2 and the conversion of cortisol to the inactive cortisone. The fourth picture shows the epidermis of RSS with abnormal thickening and cortisol still being inactivated to cortisone

16.3 RSS Management

RSS improves spontaneously over time [12]. Therefore, controlled studies are required to determine whether any medical interventions contribute to patient recovery or whether improvements seen around the time of the therapy are coincidental. No controlled studies of treatment for RSS have been published to date.

As RSS is due to the continuous application of topical steroids, the first treatment must logically be the cessation of topical steroids. However, as the diagnosis of RSS can only be made after observation of progression of symptoms following the discontinuation of topical steroids, it can be difficult to determine whether stopping topical steroids should be recommended to an individual patient.

Once the decision to stop topical steroids has been made, the next question is whether to cease treatment immediately (cold turkey) or to gradually taper the amount used. Rapaport and some doctors recommend the cold turkey approach. Other doctors advise gradually reducing the amount of topical steroids applied, and some recommend steroid injections or oral steroids to minimise intense rebound symptoms as required or desired.

When topical steroids are discontinued, steps need to be taken to reduce the risk of infections such as Kaposi varicelliform eruption and septicaemia. Bleach baths may be useful for this purpose [13]. RSS is uncommon in infants (as long-term continuous use of topical steroids is required for the condition to develop); however, occasionally it does occur. In these cases, hypoalbuminaemia and failure to thrive can be problematic and the baby should be monitored closely by a paediatrician familiar with RSS.

Expert opinion suggests moisturising agents are best avoiding when stopping topical steroids. There are some doctors who also advise limiting water intake also. Whilst this may sound irresponsible, it is based on the evidence that skin dryness leads to increased epidermal steroid production [14]. Extremely premature infants that are kept in incubators with low humidity experience a reduction in water loss from their epidermis more rapidly than those exposed to higher humidity, suggesting the low humidity assists with their skin barrier development [15].

It is possible that water restrictions can also contribute to epidermal recovery by increasing blood aldosterone levels (mineralocorticoid receptors in the epidermis bind to cortisol and work similarly to glucocorticoid receptor alpha) [16].

Moisturising has been shown to prevent AD in multiple studies [17, 18]. Thus, it may sound contradictory to advise against moisturising during RSS. However, normal skin is different to the skin seen in a patient with RSS where there has been exposure to long-term continuous use of topical steroids.

Ultraviolet therapy and tar agents are effective in RSS, although the results are not dramatic. Both therapies probably increase the amount of cortisol produced by the skin. Ultraviolet rays have been shown to increase epidermal cortisol concentration [19] and tar agents are metabolised by CYP11A1, which is a cortisol-producing enzyme.

Some doctors recommend glycyrrhizin agents in RSS patients and find these effective. As glycyrrhizin blocks 11-beta-HSD2 [20], this appears to be a logical approach. It has been reported that hyaluronic acid, which has a molecular weight of close to 100,000 daltons, helps to resist epidermal atrophy caused by topical steroid use [21].

Topical PPAR alpha agonist can control RSS symptoms (rebound) in mice [22], and clinical success has been reported in some patients too [23].

Calcineurin inhibitors and immunosuppressive drugs [3] have rarely been reported as being used to manage RSS symptoms. Dermatologists who are unfamiliar with RSS may prescribe these medications for a period before again recommending topical steroids. Doctors and patients who recognise RSS and appreciate it as a side effect of topical steroids may be reluctant to use stronger drugs with the potential for even more serious adverse effects.

Future studies are needed to determine which of these drugs (and the newer biological agents) are helpful in managing RSS symptoms.

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