Adult onset pityriasis rubra pilaris

Virendra N. Sehgal, Govind Srivastava¹, Sunil Dogra²
Dermato-Venereology (Skin/VD) Centre, Sehgal Nursing Home, Delhi, ¹Skin Institute and School of Dermatology Greater Kailash, New Delhi, ²Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence: Dr. Virendra N. Sehgal, A/6, Panchwati, Delhi-110 033, India. E-mail: drsehgal@ndf.vsnl.net.in

ABSTRACT

Pityriasis rubra pilaris (PRP) has always been an intriguing topic ever since its inception. It is a group of chronic disorders characterized by reddish orange plaques with pityriasiform scaling showing follicular keratoses, palmoplantar keratoderma, and sometimes, erythroderma. It occurs all over the world but with racial variations. Its incidence might vary and the age at onset, behavior, clinical appearance, and prognosis are considered to be very important for its classification. It may manifest either as Type I classical adult onset PRP, Type II atypical adult (onset) PRP, or Type VI PRP (HIV-associated PRP pityriasis rubra pilaris) in contrast to classical juvenile (Type III) and circumscribed juvenile (Type IV) encountered among children. Its diagnosis is largely clinical with microscopic pathology being a useful supplement, but it continues to be a therapeutic dilemma. We review the epidemiology of adult onset PRP here and take stock of the prevalent treatment options.

Key Words: Adult onset, Pityriasis rubra pilaris

INTRODUCTION

Ever since the first reported case of the disease, pityriasis rubra pilaris (PRP) has remained a consistently recorded and researched entity to date.[1-12] However, its etiology and management have remained a challenge for the treating physician. It is seen in adults (adult onset) as well as in children, and affects both the sexes. Occasionally, PRP is associated with other diseases and it was speculated that the disorder might be the result of an abnormal immune response to some antigenic stimuli.[13] However, familial occurrence of the disease might point to some genes that predispose the individual to develop this disorder after certain precipitating events.[13-17] The occurrence of this dermatosis in association with human immunodeficiency virus (HIV)/acquired immunodeficiency disease (AIDS) patients has sparked a dialogue as to whether or not it is yet another variant of PRP.[18-22]

DEFINITION

Pityriasis rubra pilaris refers to a group of chronic disorders characterized by reddish orange plaques with pityriasiform scaling showing follicular keratoses, palmoplantar keratoderma, and sometimes, erythroderma. Familial as well as acquired forms of the disease have been reported.[23]

HISTORY

Devergie has been credited with the naming of ‘pityriasis pilaris’ in 1857, which received the eponym of Devergie’s diseases.[24] However, much before that, Tarral[1] in 1835, recorded the case description of this disease in the “Rayer’s[1]-a theoretical and practical treatise on the disease of the skin” under the title of ‘general psoriasis’. Devergie stressed that Tarral’s case was an example of PRP, and observed that PRP might be confused with psoriasis. However, in 1889, Besnier[25] advanced the present day name, “pityriasis rubra pilaris.” Later, several authors[26-31] recognized that PRP was of many types, and thus suggested several working classifications.[32-37] With the advent of HIV/AIDS, its association with PRP has been noticed by many, prompting expansion of the existing classification to accommodate PRP associated with HIV as a distinct type.[38-40]
EPIDEMIOLOGY

Although PRP occurs worldwide, there are racial variations.\[2,3\] Its incidence might vary—it is 1 in 5,000 in Great Britain\[34\] and 1 in 50,000 in India\[31\] in an outpatient setting. Both the sexes are affected equally at all ages.\[14,33\] A bimodal or trimodal age distribution has been recorded with peak incidence in the 1st, 2nd and 6th decade of life.\[27,34,41-44\] The majority of the cases have been acquired\[34-42\] and familial occurrence is only sporadic (up to 6.5%).\[13-17,27,28,37,41,45,46\] Autosomal dominant inheritance with variable penetrance is usual; however, autosomal recessive inheritance has also been described.\[47\] Monozygotic twins have been observed to develop PRP.\[48\] Familial PRP usually develops in childhood while acquired PRP develops in the 5th or 6th decade of life.\[32-34\] The development of PRP in HIV/AIDS was recognized several years after its discovery, and might show peculiarities compared to classical adult PRP; it responds to antiretroviral therapy in most instances.

CLASSIFICATION

PRP was initially classified on the basis of the age at onset, behavior, clinical appearance, and prognosis by Griffiths\[34,36\] in 1980 [Table 1]. The classical (type I) adult onset PRP shows a characteristic morphology and usually resolves in 3-4 years, whereas atypical adult-onset (type II) PRP is chronic, shows ichthyosiform and lamellar scales on the palms and soles, and alopecia of varying degrees.\[2,34\] The association of PRP and HIV infection has recently been identified as type VI PRP and most of the cases have been reported in young heterosexual/homosexual men.\[22\] It has characteristically nodulo-cystic and lichen spinulosus-like lesions, poor prognosis, and is refractory to treatment.\[13-15,18-20,22,28\] However, after the study of 168 Thai patients, Piamphongsant and Akaraphant\[37\] classified the disease into four types based on the physical findings [Table 2]. However, Griffiths’\[34\] classification continues to be the mainstay in practice for delineating the disease.

ETIOLOGY

The exact cause of PRP is not known—the familial type usually has an autosomal dominant mode of inheritance,\[46\] although recessive forms have also been recorded.\[47\] Genetic factors may be important; however, family history is generally not forthcoming. Epidermal hyperactivity demonstrated by a faster growth of the nails and an increase in the thymidine labeling index from a normal 3% to a high 27%, may be observed in PRP.\[49-53\] Finzi et al, observed a decreased level of serum retinol-binding protein in 11 PRP patients and their relatives,\[54-58\] while Frazier and Hu\[59-60\] and Lowenthol\[61\] suggested that an abnormal vitamin A metabolism and/or vitamin A deficiency may play some role in PRP etiology. However, others\[62-64\] did not find any decreased levels of vitamin A; thus, no correlation between vitamin A deficiency and dyskeratosis has been established.\[65\] Interestingly, Rothman observed that vitamin A administration has often been beneficial in follicular and nonfollicular, hyperkeratotic disease even if these diseases did not originate from vitamin A deficiency.\[66\]

| Clinical type | Lesions’ distribution | Natural course | Percentage of a cases |
|---------------|-----------------------|----------------|-----------------------|
| Classical adult | Generalized | Remission in 3-4 years | 55 |
| Atypical adult | Generalized | Chronic intractable | 5 |
| Classical juvenile | Generalized | Remission in 1-2 years. | 10 |
| Circumscribed juvenile | Localized | Unpredictable | 25 |
| Atypical juvenile | Generalized | Chronic intractable | 5 |
| PRP and human immunodeficiency virus-associated type | Face and upper trunk | Refractory | On the increase |

Table 1: Pityriasis rubra pilaris-Griffith’s clinical classification\[34,36\]

| Types | 168 patients | Clinical features |
|-------|--------------|-------------------|
|       | Adult | Children |                     |
| Type I | 11 | 21 | Salmon-colored, erythematous, thick plaques on the palms and soles, extending to dorsopalmar and plantar junctions |
| Type II | 27 | 59 | Scaly erythematous patches on the elbows and knees |
| Type III | 16 | 20 | Similar patches of type II (vide supra) involving large areas of the trunk, yet not generalized |
| Type IV | 10 | 4 | Exfoliative erythroderma associated with diffuse follicular plugging |

Table 2: Piamphongsant and Akaraphant classification of pityriasis rubra pilaris
Furthermore, bacterial superantigens have recently been incriminated in triggering some skin diseases including juvenile PRP.[67-70] This has been corroborated by the detection of bacterial superantigens in the course of acute throat infections (Staphylococcus aureus and group A β Streptococcal pyogenes), simultaneous appearance of lesions conforming to the morphology of childhood onset/juvenile PRP, and the disappearance of lesions following administration of appropriate antibiotics. In addition, significant increases in peripheral blood mononuclear cell (PBMCs) counts against Staphylococcal enterotoxin B in vitro might suggest hyper-reactivity to some bacterial products, which may lead to childhood onset/juvenile PRP.[68]

**CLINICAL FEATURES**

Adult onset PRP conforms to Griffiths[34] type I classical adult and type II atypical adult classifications, the former being the most common. In contrast to childhood onset juvenile PRP,[23] adult PRP typically starts on the face and scalp and promptly spreads in the cephalocaudal direction.[2,3]

**Type I classical adult onset PRP:** It is characterized by follicular hyperkeratotic papules that coalesce into large, scaly, erythematous plaques, palmoplantar keratoderma, diffuse furfuraceous scaling of the scalp sometimes progressing into erythroderma.[2,3] The onset is usually acute and the eruptions begin on the head, neck and upper chest as discrete, follicular papules that often coalesce to form plaques with interfollicular erythema. The spread of the lesion is characteristically in the cephalocaudal direction. The face assumes a red-orange hue with mild to moderate ectropion. The affected skin is extremely rough to touch and feels like a file.[1] Prolonged erythema may cause resultant edema, and may precipitate a high output cardiac failure in the elderly. The palms and soles may acquire the appearance of a ‘hyperkeratotic sandal’, while the scalp reveals diffuse bran-like scaling. Should an erythroderma develop, a few sharply demarcated islands of unaffected skin [Figures 1A, B] are important diagnostic criteria.[2,3] Pruritus is uncommon; nail changes (if any) are marked by thickening and yellow-brown discoloration of the nail plate, subungual hyperkeratosis, and splinter hemorrhages.[2,3] Unlike psoriasis, nail dystrophy and pitting are minimal in PRP. The oral mucosa may be involved in a few patients, showing macular erythema, diffuse hyperkeratosis, and white streaks;[80] hair and teeth are normal.[2-4] Type I classical adult onset PRP runs a chronic course, three out of four cases may resolve in 1-3 years; relapses are usually uncommon.

**Type II atypical adult onset PRP:** It is an uncommon form of the disease that develops in middle-aged adults with atypical morphological features deviating from those described above. These patients show an admixture of follicular hyperkeratosis and lamellar scaling [Figures 2A, B] on their skin surface.[2-4,24,81] Areas of eczematous changes can sometimes confuse the clinical picture. The classical cephalocaudal progression is conspicuous by its absence; the occurrence of erythroderma is also unusual.

**Type VI PRP (HIV-associated PRP):** The occurrence of PRP in HIV/AIDS shows certain peculiarities[29,38-40] such as a ‘filiform’ pattern of keratosis on the face and upper trunk, accompanied by marked acne conglobata. This type is usually recalcitrant to conventional therapy and has a poor prognosis.[20-22,38-40] Other types are described in Table 1.

**ASSOCIATED FINDINGS**

Adult PRP has been found to be associated with several cutaneous and noncutaneous disorders,[82-85] the exact significance of which is a matter of speculation. The associated disorders include vitiligo, lichen planus, alopecia universalis,[12] Kaposis varicelliform eruption,[86] seronegative arthritis,[87-90] myositis,[83] myasthenia gravis,[91] hypothyroidism,[82] celiac sprue,[84] and other infections including HIV.[20,38-40] Infrequently, internal malignancies have been recorded in adult onset PRP.[92-95] However, prominent or increasing seborrhoeic keratoses seen in erythrodermic PRP does not necessarily imply an underlying malignancy.[85,96] An intense degree of erythema in erythrodermic PRP predisposes the individual to photosensitivity and worsening of the erythema has also been recorded with UVA and UVB.[97-99]

**HISTOPATHOLOGIC FINDINGS**

Adult onset PRP displays distinctive histopathological findings, which may differ according to the stage and evolution of the lesions.[2,3] The salient criteria include: (a) alternating orthokeratosis and parakeratosis in both the vertical and horizontal directions, (b) hypergranulosis, (c) irregular acanthosis apparent in the form of short and broad rete-ridges, (d) thick suprapapillary plates, and (e) a sparse to moderate lymphocytic perivascular infiltrate in the dermis[27,42,49,71,100] [Figure 3]. The hair follicles are dilated and filled with a dense, horny plug [Figure 4]. Munro’s microabscesses and suprapapillary thinning are conspicuously absent. The differential diagnosis may often be difficult in erythrodermic patients.
Walsh et al. [101] found that dermatopathologist are the least (25%) accurate when scanning the sections prepared from biopsies of erythroderma of PRP origin. The dermis shows dilated capillaries with a mild to moderate infiltrate of lymphocytes and histiocytes. Acantholysis and focal acantholytic dyskeratosis have recently been recorded in adult PRP. [94,102-104] These histological parameters are unique and different from those seen in psoriasis; Magro and Crowson [43] found these features in 23 of the 32 biopsies from PRP. However, they were not found in any of the specimens of psoriasis.

Porter and Shuster [105] have been credited with the demonstration of increased epidermal replacement after they found an increase in the uptake of amino acids by the PRP lesions. Later on, several in vivo and in vitro autoradiography studies using titrated thymidine confirmed an increase in the labeling index of PRP epidermal cells when compared with normal, reflecting increased cell proliferation. [42,49,50,51,53,106] Electron microscopy revealed a decrease in the number of tonofilaments, desmosomes, and enlarged intercellular spaces. [49,107] The corneocytes are fusiform and show numerous pits. [107] Evidence of parakeratosis of the stratum corneum is seen as lipid-like vacuoles, incomplete keratinization, and remnants of nuclei. [58,107]

LABORATORY FINDINGS

Hematological and laboratory test results are usually
within normal limits; the main emphasis remains on the histopathology. Plasma vitamin A and carotenoid levels are normal,[62-64] although retinal-binding protein may be low[54] or normal.[55-58] Direct immunofluorescence tests with antibodies to human IgG, IgM, IgA and complement C3 were found to be negative in 15 adult PRP patients by Niemi.

### Table 3: Treatment options in adult onset pityriasis rubra pilaris

| Author(s) | Years | Recommended drug(s) | Dosage | Response / Result | Number of patients |
|-----------|-------|---------------------|--------|--------------------|--------------------|
| Petter[131], Gunther[132], Gunther S, Alston W[133], Randle, Diaz-Perez, Winkelmann[134], Winkelmann, Thomas, Randle[135], Kellum[136], Murray, Gilgor, Lazarus[137], Anonymous[138] | 1936, 1983, 1971 | Vitamin A | 1,000,000 IU/per day x/2 weeks | Good | 2 |
| Ayres, Mihan, Scribner[139] | 1979 | Vitamins A and E | 500,000 IU + 200-400 IU | Synergism of vitamins A and E | A report |
| Skinner, Rosenberg, | 1981 | Cod liver oil | 1-3 mL/day | Worthwhile | Case report / letter |
| Pucevich, Kaplan[140] | 1941 | Habibul liver oil | 1-3 mL/day | Good | - |
| Webster and Falk[175] | 1952 | ACTH + Vitamin A | 1,000,000 IU of Vitamin A + 10-20 units Adreno cortico trophic hormone/week | Favorable | 2 patients |
| Watt and Jilson[179] | 1965 | Penicillin and antitubercular drugs | Penicillin V 1 g/day plus usual anti tubercular regimen | Equivocal | 6 patients |

### Modern treatments for adult onset PRP

| Author(s) | Years | Recommended drug(s) | Dosage | Response / Result | Number of patients |
|-----------|-------|---------------------|--------|--------------------|--------------------|
| Kirby, Watson R[154] | 2000 | Retinoid + UV light | Acetretin + UVA: 1 (0.75 mg/kg/day) acetretin + narrowband UV-B (Re-TL-01) | Favorable | Case report/ letter |
| Ehnis, Kielh, Kapp, Weiss[157] | 1999 | PUVA | Extracorporeal photo-chemotherapy | Mild to moderate good in erythroderma | Case report/ letter 1 |
| Hofer, Mullegger, Kerf, Wolf[156] Neess, Hinrichs, Dissemend, Herrmann, Poswig, Servera-Llanaras et al[161] | 2000 | Methotrexate | 5-30 mg/week | Equivocal good to mild | Case report/ review |
| Lim and Tham[162] | 1991 | Systemic prednisolone | 20-60 mg/day | Useful only in some cases | 4 |
| Brice, Spencer[163] | 1985 | Stanozolol | 2 mg/day | Good result in some cases | Letter case report |
| Pavlidakey, Hashimoto, Savoy, Heller, Iacobelli, Barfield[164] | 1985 | Calcipotriol | Topical ointment applied daily | Same cases may respond | Case report/ letter |
| van de kerkhof and de Jong[181] Thiers[182] | 1991, 1997 | Fumaric acid | *Recommended dosages | Claimed to be useful | - |
| van de kerkhof and de Jong[183] Thiers[184] | 1991, 1997 | Extracorporeal photo-chemotherapy (ECP) | 2 Joule/cm², monthly interval on 2 consecutive days | Good results in isolated cases | - |
et al.\[^{[42]}\] However, immuno-electrophoresis of the scales from PRP demonstrated the presence of only IgG, while psoriatic scales had IgG, IgA and C_{3}\[^{[108]}\]. Takematsu et al.\[^{[109,110]}\] recorded normal levels of leukotriene B_{4} but low levels of anaphylotoxins in scale extracts from PRP. Other studies have been done on HLA typing,\[^{[42]}\] direct immunofluorescence,\[^{[42]}\] keratin monoclonal antibodies,\[^{[15]}\] parathyroid hormone levels,\[^{[111]}\] and a western blot analysis of the skin,\[^{[15]}\] but these studies only have academic significance.

**DIAGNOSIS**

Until the disease is well-developed, it may be difficult to diagnose with full confidence. However, repeated observations and a few biopsies may confirm the diagnosis.\[^{[2,4,24,112-116]}\] Atypical (type II) PRP may be more difficult to diagnose than classical adult onset (type I) PRP. Follicular hyperkeratosis on the back of the fingers, orange-colored eruptions with intervening areas of normal skin ‘islands of sparing’ and/or palmoplantar keratoderma are features of classical adult onset PRP; they are ill defined in atypical adult PRP.\[^{[2,4,117]}\] The differential diagnosis of adult onset PRP usually includes psoriasis,\[^{[2,4,118]}\] The absence of Auspitz and candle grease signs is an instant clinical diagnostic clue.\[^{[2,3]}\] Erythrodermic PRP can be confused with other forms of erythroderma\[^{[119]}\] and skin biopsy of such patients can confirm PRP only on an exclusion basis.\[^{[109]}\] Arthropathic PRP is unusual to record.\[^{[120]}\] Resolving PRP may mimic seborrhoeic dermatitis\[^{[2]}\] or erythema gyratum repens.\[^{[17,121]}\] PRP may be a cutaneous marker of internal malignancy,\[^{[92,93,95,122]}\] leukemia,\[^{[93]}\] metastatic carcinoma,\[^{[92]}\] or Sezary syndrome\[^{[123]}\] in adults, which may follow after a variable length of time. Interestingly, cutaneous T-cell lymphoma and Sezary’s syndrome also form a differential diagnosis of erythrodermic PRP.\[^{[124,125]}\] Rarely, dermatomyositis may develop skin eruptions akin to the adult onset PRP.\[^{[126-130]}\] Heteroduplex analysis of T-cell receptor gamma gene arrangements may be a newer adjuvant diagnostic tool in skin biopsies from erythrodermas.\[^{[128]}\]

**TREATMENT OPTIONS**

The diagnosis and treatment of PRP have always been a source of great interest. There is no acclaimed treatment for PRP at present. Thus, affected individuals often visit and change many treating dermatologists to alleviate their signs and symptoms. More often than not, it is an exercise in futility as the treating physician/dermatologist too is in dilemma. Several treatment\[^{[131-191]}\] options have been in vogue and are tabulated below [Table 3].

Narrowband UV-B with oral retinoids has been useful in some cases.\[^{[182,187]}\] Topical calcipotriol\[^{[138]}\] and tacalcitol have also given promising results in some patients. HIV-associated PRP is more recalcitrant but antiretroviral drug therapy has caused alleviation of the symptoms and may even cause complete regression in such patients.\[^{[138]}\] Methotrexate has been found to be moderately effective. In an attempt to explore an ideal therapy, newer treatment options like biologicals (infliximab), calineurin inhibitors (pimecrolimus) etc. are being tried in PRP.\[^{[192,193]}\] The use of emollients to symptomatically improve the condition may also be useful. It is imperative to record at this point in time, that several treatment options that have been used so far may not be satisfactory as no organized drug trials are available. Nevertheless, isotretinoin, a retinoid, seems to be a plausible option.\[^{[49,154,189-193]}\]

The historical and epidemiological perspectives of adult onset PRP as well as its etiology have been described. Microscopic pathology and its variations have been clearly defined, emphasizing its role in supplementing clinical diagnosis and treatment has been facilitated by the inclusion of a table for decision-making.

### REFERENCES

1. Tarral C. General psoriasis-desquamation from the parts covered by hair. In: Rayer P, editor. A theoretical and practical treatise on the diseases of the skin. 2nd ed, London: Bailliere; 1835. p. 648-9.
2. Griffiths WA, Judge MR, Leigh IM. Disorders of keratinization-pityriasis rubra Pilaris. In: Champion RH, Burton JL, Burns DA, et al, editors. Text Book of dermatology, 6th ed. London: Blackwell Science; 1988. p. 1539-45.
3. Gold Smith LA, Baden HP. Pityriasis rubra pilaris. In: Freeberg IM, Eisen AZ, Wolff K, et al, editors. Dermatology in general medicine. Vol 1 6th ed. London: Mc-Graw Hill Publication; 2003. p. 442-4.
4. Albert MR, Mackool BT. Pityriasis rubra pilaris. Int J Dermatol 1999;38:1-11.
5. White KL. Pityriasis rubra pilaris. Dermatol Online J 2003;9:6.
6. Vijayalakshmi AM, Malika A. Pityriasis rubra pilaris. Indian Pediatr 2003;40:432-3.
7. Selvaag E, Haederstel M, Thomsen K. Pityriasis rubra pilaris: A retrospective study of 12 patients. J Eur Acad Dermatol Venereol 2000;14:514-5.
8. Sehgal VN, Bajaj P, Jain S. Pityriasis rubra pilaris -report of four cases. J Dermatol 2000;27:174-7.
9. Sorensen KB, Theshtrup-Pedersen K. Pityriasis rubra pilaris: A retrospective analysis of 43 patients. Acta Derm Venereol 1999;79:405-6.
10. Varma S, Logan RA. Exanthematic pityriasis rubra pilaris. Br J Dermatol 1999;141:769-71.
disorders evaluated through PCNA/ Cyclin immunolabelling and AGNOR counting. Acta Derm Venereol 1993;73:370-5.

53. Griffiths WA, Piersis R. Pityriasis rubra pilaris: An autoradiographic study. Br J Dermatol 1982;107:665-7.

54. Finzi AF, Altomare G, Bergamaschini L, Tucci A. Pityriasis rubra pilaris and retinol binding protein. Br J Dermatol 1981;104:253-6.

55. Brice SL, Spencer SK. Stanozolol in the treatment of pityriasis rubra pilaris. Arch Dermatol 1983;110:1105-6.

56. Van Voorst Vader PC, Van Oostveen F, Houthoff HJ, Marrink J. Pityriasis rubra pilaris, Vitamin A and Retinol binding protein: A case study. Acta Derm Venereol 1984;64:30-2.

57. Stoll DM, King LE Jr, Chytil F. Serum levels of retinol binding protein in patients with pityriasis rubra pilaris. Br J Dermatol 1983;108:375.

58. Kanerva L, Lauharanta J, Niemi KM, Lassus A. Ultrastructure of pityriasis rubra pilaris with observation during retinoid treatment. Br J Dermatol 1983;108:553-63.

59. Frazier CN, Hu CK. Cutaneous lesions associated with a deficiency of vitamin A in man. Arch Intern Med. 1931;48:507-14.

60. Frazier CN., Hu CK. Nature and distribution according to age of cutaneous manifestation of vitamin A deficiency: A study of 207 cases. Arch Dermatol Syphilol 1936;33:3825-52.

61. Lowenthal LJ. A new cutaneous manifestation in the syndrome of vitamin A deficiency. Arch Dermatol Syphilol 1933;28:700-8.

62. Cornbleet T. Liver Vitamin A in Darier's and Davergies disease. J Invest Dermatol 1954;23:371-3.

63. Gross DA, Landay JW, Newcomer VD. Pityriasis rubra pilaris: report of a case and analysis of the literature. Arch Dermatol 1969;99:710-6.

64. Griffiths WA. Vitamin A and pityriasis rubra pilaris: A review of diagnosis and treatment. J Am Acad Dermatol 1982;7:555.

65. Mier PD, Van Den Hurk J, Van Rossen E. Plasma vitamin A levels in dyskeratosis. Br J Dermatol 1975;92:273-5.

66. Rothman S. Physiology and biochemistry of the skin. Chicago: University of Chicago Press; 1954. p. 382-90.

67. Skov L, Baadsgaard O. Superantigens: Do they have a role in skin diseases? Arch Dermatol 1995;131:829-32.

68. Yamamoto T, Yokoyama A. Lymphocyte response to superantigen in a patient with childhood-onset pityriasis rubra pilaris. Int J Dermatol 1999;38:639-40.

69. Betlloch I, Ramon R, Silvestre JF, Carnero L, Albares MP, Banuls J. Acute juvenile pityriasis rubra pilaris: A super-antigen mediated disease? Pediatr Dermatol 2001;18:411-4.

70. Barr RJ, Young EM Jr. Psoriasiform and Papulosquamous disorders. J Cutan Pathol 1985;12:412-25.

71. Mohrenschlager M, Abeck D. Further clinical evidence for involvement of bacterial superantigens in juvenile pityriasis rubra pilaris (PRP): Report of two new cases. Pediatr Dermatol 2002;19:569.

72. Shahidullah H, Aldridge RD. Changing forms of juvenile pityriasis rubra pilaris. Clin Exp Dermatol 1994;19:254-6.

73. Pankaj Rk, Vinod Kumar CH, Rajendran V, Ramesh K, Anandadasan PK, Bhatia VN, et al. Pityriasis rubra pilaris with leprophobia. Int J Lepro Other Micobact Dis 1987;55:555-6.
manifestation of leukemia. Cutis 1983;31:100-2.
94. Tannenbaum CB, Billick RC, Srolovitz H. Multiple cutaneous malignancies in a patient with pityriasis rubra pilaris and focal acantholytic dyskeratosis. J Am Acad Dermatol 1996;35:781-2.
95. Huynh NT, Hunt MJ, Cachia AR, Veness MJ. Merkel cell carcinomas and multiple cutaneous squamous cell carcinomas in a patient with pityriasis rubra pilaris. Australas J Dermatol 2002;43:48-51.
96. Schweggele LE, Rampen FH. Eruptive seborrheic keratoses associated with erythrodermic pityriasis rubra pilaris: Possible role of retinoid therapy. Acta Dermato Venereol 1988;63:443-5.
97. Kaskel P, Peter RU, Kerscher M. Phototesting a phototherapy in pityriasis rubra pilaris. Br J Dermatol 2001;144:430.
98. Yaniv R, Barzilai A, Trau H. Pityriasis rubra pilaris is exacerbated by UV-B phototherapy. Dermatology 1994;189:213.
99. Marguery MC, Durand-Malgouyres C, Bayle-Lebey P, Dupin P, Bazex J. Photosensitive and phototrigged: Pityriasis Rubra Pilaris. Photodermatol Photomol 1994;104:2.
100. Lever WF, Schaumberg Lever G. Pityriasis Rubra Pilaris. In: Lever WF, ed. Suggested reading. 7th ed. Philadelphia: J.B Lipponcott; 1996. p. 176-8.
101. Walsh NM, Prokopetz R, Tron VA, Sawyer DM, Watters AK, Murray S, et al. Histopathology in erythroderma - review of a series of cases by multiple observers. J Cutan Pathol 1994;21:149-23.
102. Cowen R, O’Keefe R. Pityriasis rubra pilaris and focal acantholytic dyskeratosis. Australas J Dermatol 1997;38:40-1.
103. Howe K, Foresman P, Griffin T, Johnson W. Pityriasis rubra pilaris with acantholysis. J Cutan Pathol 1996;23:270-4.
104. Duke RA, Barrett MR, Salazer JE, Scott RL, Sebes JE. Acroosteolysis secondary to Pityriasis rubra pilaris. AJR Am J Roentgenol 1987;149:1082-3.
105. Porter D, Shuster S. Epidermal renewal and amino acids in psoriasis and pityriasis rubra pilaris. Arch Dermatol 1968;98:2339-43.
106. Marks R, Griffiths A. The epidermis in Pityriasis rubra pilaris: A comparison with psoriasis. Br J Dermatol 1973;89:19-20.
107. Amer M, Mostafa FE, Tossen Z, Nasr AN. Corneocytes in scalp parakeratotic disease. Int J Dermatol 1996;35:417-21.
108. Kaneko F, Muramatu R, Takahashi Y, Miura Y. Extractable immune complex in soluble substance from psoriatic scale. Arch Dermatol Res 1984;276:45-51.
109. Takematsu H, Teruni T, Tagami H. Demonstration of leukotriene B4 in the scale extracts of psoriasis and inflammatory pustular dermatoses: Correlation with leukocyte chemotactic activity and C5a anaphylatoxin. Acta Dermato-Venereol (Stockh)1986;66:5-10.
110. Takematsu H, Ohkouchi K, Tagami H. Demonstration of Anaphylatoxins C3a, C4a, C5a in the scale of psoriasis and inflammatory pustular dermatoses. Br J Dermatol 1986;114:1-11.
111. Milstone LM, Ellison AF, Insogna KL. Serum parathyroid hormone level is elevated in some patients with disorders of keratinization. Arch Dermatol 1992;128:926-30.
112. Westerhof W, Dingemans KP. The morphology of keratohyalin granules in orthokeratotic and parakeratotic skin and oral mucosa. Int J Dermatol 1987;26:508-13.
113. Kao GF, Sulica VL. Focal acantholytic dyskeratosis occurring in pityriasis rubra pilaris. Am J Dermatopathol 1989;11:172-6.
114. Kariniemi AL, Virtamme I. Altered Keratin expression in benign malignant skin disease revealed with monoclonal Antibodies. Am J Dermatopathol 1989;11:202-8.
115. Gandarillas A, Goldsmith LA, Gschmeissner S, Leigh, I.M, Watt, F.M. Evidence that apoptosis and terminal differentiation of epidermal keratinocytes are distinct process. J Exp Dermatol 1999;8:71-9.
116. Hashimoto K, Fedoronko L. Pityriasis rubra pilaris with acantholysis and lichenoid histology. Am J Dermatopathol 1999;21:491-3.
117. Caplan SE, Lowitt MH, Kao GF. Early presentation of pityriasis rubra pilaris. Cutis 1997;60:291-6.
118. Belew-Noah PW, Rosenberg WE, Zabriskie JB, Skinner RB Jr, Henson TH, Beard GB. Microbial association and response to antimicrobial seen in a psoriasis clinic. Adv Exp Med Biol 1997;418:157-9.
119. Sehgal VN, Srivastava G. Exfoliative dermatitis: A prospective study of 80 patients. Dermatologica 1986;173:278-84.
120. Fiallo P, Tagliapietra AG, Santoro G. Arthropathic pityriasis rubra pilaris. Br J Dermatol 1996;134:1154-5.
121. Cheesbrough MJ, Williamson DM. Erythema gyratum repens: A stage in the resolution of pityriasis rubra pilaris? Clin Exp Dermatol 1985;10:466-71.
122. Sharma S, Weiss GR, Paulger B. Pityriasis rubra pilaris as a initial presentation of hepatocellular carcinoma. Dermatology 1997;194:166-7.
123. Roger J, Burg G, Miller K, Lanz U. Pityriasis rubra pilaris-artiges Vorstadium eines Sézary-Syndroms (Pityriasis rubra pilaris the precursor of a Sézary’s syndrome). Z Hautkr 1991;66:1046-50.
124. Westfried M, Rosenthal JC, Coppola A, Rapp Y. Sezary syndrome presenting as follicular dermatosis. Cutis 1982;29:920-6.
125. Schmoeckel C, Burg G, Hoffmann-Fezer G, Stolz W, Löhrs U, et al. Cutaneous immunoblastic T-cell Lymphoma. Arch Dermatol Res 1982;274:141-54.
126. Lupton JR, Figueueroa P, Berberian BJ, Sulica VI. An Unusual presentation of Dermatomyositis - the type wong variant revisited. J Am Acad Dermatol 2000;43:908-12.
127. Requena L, Grilli R, Soriano L, Escalonilla P, Farina C, Martin L. Dermatomyositis with a pityriasis rubra pilaris-like eruption: A little-known distinctive cutaneous manifestation of dermatomyositis. Br J Dermatol 1997;136:768-71.
128. Cherry S, Mraz S, Su L, Harvell, J. Kohler S. Heteroduplex analysis of T-cell receptor γ gene rearrangement as an adjuvant diagnostic tool in skin biopsies for erythroderma. J Cut Am Pathol 2001;28:351-5.
129. Dicken CH. Treatment of classic Pityriasis rubra pilaris. J Am Acad Dermatol 1994;31:979-9.
130. Shackelford KE, Belzito DV. The etiology of allergic-appearing
foot dermatitis: A 5 year retrospective study. J Am Acad Dermatol 2002;47:715-21.
131. Petter MF. Pityriasis Rubra Pilaris, with particular reference to vitamin medication and dietary control. Penn Med J 1936;39:864-6.
132. Gunther S. Topical administration of vitamin A acid (retinoic acid) in palmar keratoses: Callosities, hyperkeratotic eczema, hypertrophic lichen planus, pityriasis rubra pilaris. Dermatologica 1972;145:344-7.
133. Gunther S, Alston W. follicular keratosis. Pilot slides of serum levels of vitamin A, and LFT during administration of retinoic acid in kyrle’s diseases, Pityriasis Rubra Pilaris and Darier’s disease. Dermatologica 1973;147:274-83.
134. Randle HW, Diaz-Perez JL, Winkelmann RK. Toxic doses of vitamin A for pityriasis rubra pilaris. Arch Dermatol 1980;116:888-92.
135. Winkelmann RK, Thomas JR. Pityriasis Rubra Pilaris controlled by synergism of vitamin A and E with dermatologic application. Cutis 1979;23:600-3.
136. Ayres S Jr, Mihan R, Scribner MD. Synergism of Vitamin A and E with dermatologic application. Cutis 1979;23:600-3.
137. Murray JC, Gilgor RS, Lazarus GS. Serum triglyceride elevation following high dose Vitamin A treatment for pityriasis rubra pilaris. J Am Acad Dermatol 1989;20:126-8.
138. Brunsting LA, Sheard C. Dark adaptation in pityriasis rubra pilaris. Arch Dermatol 1999;140:715-21.
139. Skinner RB Jr, Rosenberg EW, Pucevich MV, Kaplan RJ. Vitamin A and E. J Am Acad Dermatol 1981;27:4-6.
140. Weiner AL, Levin AA. Pityriasis rubra pilaris of familial type of keratinization: Results of an open study. J Am Acad Dermatol 1991;24:982-6.
141. Blaustein PA, Winkelmann RK. Acitretin in the treatment of severe disorders of keratinization: Results of an open study. J Am Acad Dermatol 1991;24:982-6.
142. Blanchet-Bardon A. Pityriasis rubra pilaris. Cutis 1993;52:274-8.
143. Van Dooren-Greebe RJ, Van-De-Kerkhof PC. Extensive extraspinial hyperostosis after long term oral retinoid treatment in a patient of pityriasis rubra pilaris. J Am Acad Dermatol 1995;33:232-5.
144. Blachet-Bardon A, Nazzaro V, Rognin C, Geiger JM, Puissant A. Acitretin in the treatment of severe disorders of keratinization: Results of an open study. J Am Acad Dermatol 1991;24:982-6.
145. Basta Juzbasic A, Dobric I, Schonwald D. Acitretin in the treatment of pityriasis rubra pilaris. Retinoids, Today Tomorrow 1994;357-10.
146. Peck GL, Yoder FW, Olsen TG, Pandya MD, Butkus D. Treatment of Darier’s Disease, lamellar ichthyosis: Pityriasis rubra pilaris, cystic acne and basal cell carcinoma with oral 13cis retinoic acid. Dermatologica 1978;157:11-2.
147. Gilgor RS, Chiaramonti A, Goldsmith LA, Lazarus GS. Evaluation of 13-cis retinoic acid in lamellar ichthyosis, pityriasis rubra pilaris and Darier’s diseases. Cutis 1980;25:380-5.
148. Farb RM, Lazarus GS, Chiaramonti A, Goldsmith LA, Gilgor RS, Balakrishnan CV. The effect of 13-Cis retinoic acid on epidermal lysosomal hydrolase activity in Darier’s diseases and Pityriasis Rubra Pilaris. J Invest Dermatol 1980;75:233-5.
149. Goldsmith LA, Weinrich AE, Shupack J. Pityriasis rubra pilaris response to 13-cis retinoic acid (Isotretinoin). J Am Acad Dermatol 1982;6:710-5.
150. Becker K. Isotretinoin: A review. Ariz Med 1983;40:88-90.
151. Dicken CH. Isotretinoin treatment of pityriasis rubra pilaris. J Am Acad Dermatol 1987;16:297-301.
152. Fleissner J, Happle R. Etretinate in the treatment of Juvenile pityriasis rubra pilaris. Arch Dermatol 1981;117:749-50.
153. Kirby B, Watson R. Pityriasis rubra pilaris treatment with acitretin and narrow band ultraviolet B (Re-TL-01). Br J Dermatol 2000;142:37-54.
154. Hofer A, Mullerger R, Kerl H, Wolf P. Extracorporeal photo chemotherapy for the treatment of erythrodermic pityriasis rubra pilaris. Arch Dermatol 1999;135:475-6.
155. Kaskel P, Grundmann-Kollmann M, Schiller PL, Krahn G, Pillekamp H, Peter RU, et al. Bath PUVA as a treatment for pityriasis rubra pilaris provoked by ultraviolet B. Br J Dermatol 1999;140:769-70.
156. Khoo L, Asawannon P, Grevelink SA, Taylor CR. Narrow band UVB- associated lesional blisters in pityriasis rubra pilaris. J Am Acad Dermatol 1999;41:1803-4.
157. Neess CM, Hinrichs R, Dissemond J, Herrmann G, Poswig A, Weiss J. Combined UV A1 radiation and acitretin therapy as a treatment option for pityriasis rubra pilaris. Br J Dermatol 2000;142:574-5.
158. Herbst RA, Vogelbruch M, Ehnis A, Keich P, Kapp A, Weiss J. Combined UV A1 radiation and acitretin therapy as a treatment option for pityriasis rubra pilaris. Br J Dermatol 2000;142:574-5.
159. Reder A, Mullerger R, Kerl H, Wolf P. Extracorporeal photo chemotherapy for the treatment of erythrodermic pityriasis rubra pilaris. Arch Dermatol 1999;135:475-6.
160. Kaskel P, Grundmann-Kollmann M, Schiller PL, Krahn G, Pillekamp H, Peter RU, et al. Bath PUVA as a treatment for pityriasis rubra pilaris provoked by ultraviolet B. Br J Dermatol 1999;140:769-70.
161. Khoo L, Asawannon P, Grevelink SA, Taylor CR. Narrow band UBV- associated lesions blisters in pityriasis rubra pilaris. J Am Acad Dermatol 1999;41:1803-4.
162. Reder A, Mullerger R, Kerl H, Wolf P. Extracorporeal photo chemotherapy for the treatment of erythrodermic pityriasis rubra pilaris. Arch Dermatol 1999;135:475-6.
163. Kaskel P, Grundmann-Kollmann M, Schiller PL, Krahn G, Pillekamp H, Peter RU, et al. Bath PUVA as a treatment for pityriasis rubra pilaris provoked by ultraviolet B. Br J Dermatol 1999;140:769-70.
164. Neess CM, Hinrichs R, Dissemond J, Herrmann G, Poswig A, Servera-Llanras M et al. Treatment of pruritus by capsaicin in a patient with Pityriasis Rubra Pilaris receiving RE-PUVA therapy. Clin Exp Dermatol 2000;25:209-11.
165. Lamar L, Gaethe G. Pityriasis rubra pilaris. Arch Dermatol 1964;89:515-22.
166. Anderson FE. Pityriasis rubra pilaris treated with methotrexate. Australas J Dermatol 1966;8:183-5.
167. Brown J, Perry HO. Pityriasis rubra pilaris- treatment with folic acid antagonists. Arch Dermatol 1966;94:366-8.
168. Parish LC, Woo TH. Pityriasis rubra pilaris in Korea- treatment with methotrexate. Dermatologica 1969;139:299-403.
169. Knowles WR, Chernosky ME. Pityriasis rubra pilaris - prolonged treatment with methotrexate. Arch Dermatol 1970;102:603-12.
170. Weinstein GD. Methotrexate. Ann Intern Med 1977;86:199-204.
171. Duncan KO, Imaeda S, Milstone LM. Pneumocystis carinii pneumonia complicating methotrexate treatment of pityriasis rubra pilaris. J Am Acad Dermatol 1998;39:276-8.
Hunter GA, Forbes IJ. Treatment of pityriasis rubra pilaris with azathioprine. Br J Dermatol 1972;87:42-5.

Gendler E. Azathioprine for use in Dermatology. J Dermatol Surg Oncol 1984;10:462-4.

Rosenbach A, Lowe NJ. Pityriasis rubra pilaris and cyclosporine. Arch Dermatol 1993;129:1346-8.

Usuki K, Sekiyama M, Schimada T, Shimada S, Kanzaki T. Three cases of pityriasis rubra pilaris successfully treated with cyclosporine A. Dermatology 2000;200:24-7.

Meyer P, van Voorst Vader PC. Lack of effect of cyclosporine A in pityriasis rubra pilaris. Acta Derm Venerol 1989;69:272.

Webster JR, Falk AB. Pityriasis rubra pilaris; clinical and laboratory observation on combined treatment with corticotropin and Vitamin A. AMA Arch Dermatol Syphilol 1952;65:685-700.

Binnick SA. Pityriasis rubra pilaris responding to aminonicotinamide. Arch Dermatol 1978;114:1348-9.

Griffiths A, Ralfs I. Aminonicotinamide in pityriasis rubra pilaris. Arch Dermatol 1981;117:127.

Irgang S. Pityriasis rubra pilaris responsive to ascorbic acid. Australas J Dermatol 1968;9:211-7.

Watt TL, Jillson OF. Pityriasis rubra pilaris: Penicillin and antituberculous drugs as possible therapeutic agents. Arch Dermatol 1965;92:428-30.

Pavlidakey GP, Hashimoto K, Savoy LB, Heller GL, Iacobelli D, Barfield L. Stanozolol in the treatment of pityriasis rubra pilaris. Arch Dermatol 1985;121:546-8.

van de Kerkhof PC, de Jong EM. Topical treatment with the Vitamin D3 analogue MC903 improves pityriasis rubra pilaris: Clinical and immunochemical observation. Br J Dermatol 1991;125:293-4.

Van de Kerkhof PC, Steijlen PM. Topical treatment of pityriasis rubra pilaris with calcipotriol. Br J Dermatol 1994;130:675-8.

Thiers BH. The use of topical calcipotriene-calcipotriol in conditions other than plaque-type psoriasis. J Am Acad Dermatol 1997;37:S69-71.

Coras B, Vogt TH, Ulrich H, Landthaler M, Hohenleutner U. Fumaric acid esters therapy: A new treatment modality in pityriasis rubra pilaris? Br J Dermatol 2005;152:388-9.

Haenssle HA, Bertsch HP, Emmert S, Wolf C, Zutt M. Extracorporeal photochemotherapy for the treatment of exanthematic pityriasis rubra pilaris. Clin Exp Dermatol 2004;29:244-6.

Sehgal VN, Srivastava G, Aggarwal AK, Sardana K, Jain M. Efficacy of isotretinoin in pityriasis rubra pilaris: Unapproved use. Int J Dermatol 2006;45:1238-40.

Okano M. Assessment of the clinical effect of topical tacalcitol on ichthyoses with retentive hyperkeratosis. Dermatology 2001;202:116-8.

Gonzalez-Lopez A, Velasco E, Pozo T, Del Villar A. HIV-associated pityriasis rubra pilaris responsive to triple antiretroviral therapy. Br J Dermatol 1999;140:931-4.

Griffiths WA. Pityriasis rubra pilaris: An historical approach: 2. Clinical features. Clin Exp Dermatol 1976;1:37-50.

Sardana K, Sehgal VN. Retinoids: Fascinating up-and-coming scenario. J Dermatol (Tokyo) 2003;30:355-80.

Goldsmith LA, Weinrich AE, Shupack J. Pityriasis rubra pilaris: Type I adult-onset pityriasis rubra pilaris response to 13-cis-retinoic acid (isotretinoin). J Am Acad Dermatol 1982;6:710-5.

Manoharan S, White S, Gumparthy K. Successful treatment of type I adult-onset pityriasis rubra pilaris with infliximab. Australas J Dermatol 2006;47:124-9.

Gregoriou S, Argyriou G, Christofidou E, Vranou A, Rigopoulos D. Treatment of pityriasis rubra pilaris with pimecrolimus cream 1%. J Drugs Dermatol 2007;6:340-2.