Confluent and Reticulate Papillomatosis: A Retrospective Study from southern India

Abstract

Background: Confluent and reticulate papillomatosis (CRP) is an uncommon benign, acquired keratinization disorder. Studies on this disorder are lacking except for a few case reports and there is a paucity of Indian literature on the condition. Objectives/Methods: To study and describe the various morphological patterns and histopathological findings, as well as assess the response to treatment of 30 patients diagnosed with CRP. Results: Thirty patients with a diagnosis of confluent and reticulate papillomatosis were included in the study. The male to female ratio was 1:1.5. Mean age at onset of skin eruptions was 27.3 years and mean duration of skin eruptions was 8.2 months. Most of the patients (60%) were asymptomatic. The majority (66.7%) had lesions distributed over upper trunk. Two-thirds of patients had typical brown macules in confluent and reticulate pattern. KOH mount was done in 24 cases and was positive in three cases (12.5%) for yeast-like hyphae. Biopsy demonstrated variable degrees of hyperkeratosis, papillomatosis, and moderate acanthosis. Thirteen out of eighteen patients on minocycline showed complete clearance within 3 weeks and three patients had more than 50% improvement at the end of 3 weeks. Doxycycline showed satisfactory response but results were less satisfactory with azithromycin. Conclusion: CRP is an uncommon condition. There is a paucity of large studies in Indian literature. The present study highlights such a large cohort of cases. Prevalence of CRP was more in female in contrast to western studies. Association of CRP with hyperthyroidism was described in many studies but the present study highlights the association with hypothyroidism. Morphological variants like shiny atrophic lesions, verrucous lesions, and involvement of atypical sites like forearm have been described. Role of minocycline in the management of chronic and recurrent cases has been reinforced.

Keywords: Confluent and reticulate papillomatosis, minocycline, reticulate dermatoses

Introduction

Confluent and reticulate papillomatosis (CRP) is an uncommon disease first described by Gougerot and Carteaud in 1927.[1] It is a benign acquired keratinization disorder that usually presents sporadically, with onset typically occurring in young adulthood. It clinically manifests as scaly, dull, brownish, centrally confluent, and peripheral reticulate macules and papules that coalesce to form patches on the upper trunk and neck.[2] The etiology is poorly understood, but an aberrant host reaction to Malassezia furfur or Dietziasp. has been proposed.[3] Other presumed etiological factors are abnormal keratinization, endocrine problems (e.g., insulin resistance and hypothyroidism), androgenetic predisposition, but none has been clearly shown to be causative.

Thus, there is no etiology-based therapy for this condition.[4-6] Oral drugs like minocycline, doxycycline, and isotretinoin, and topical agents like tretinoin, tazarotene, calcipotriol, selenium sulfide, and tacroldol have been tried with various success rates. CRP is uncommon and studies on this skin condition have not been published in our population. In this retrospective study, we attempt to describe the clinical and histopathological findings, as well as response to treatment of 30 patients diagnosed with CRP.

Methods

Retrospective analysis of the records of patients who attended the outpatient dermatology department at Mandya Institute of Medical Sciences, Mandya, Karnataka, and M.S. Medical College, Hubli, Karnataka, for the period of June 2016 and May 2018 was included after obtaining}
ethical clearance from institutional ethical committee. The diagnosis was done based on clinical features. KOH mount and histopathology were done to exclude other similar dermatosis when in doubts. Details of the recruitment process are shown in Figure 1. The patients who had completed treatment were only included in the study. The patients who lost to follow-up for a period of 1 year were excluded. Retrospective data related to gender, age, and duration of disease, site and morphology of lesions, associated symptoms/disorders, fungal stain, skin biopsy findings, and therapeutic modalities over a period of 2 years were collected.

Results

The clinical data of 30 patients are summarized in Table 1. The male to female ratio was 1:1.5 (12 males and 18 females). The mean age at onset of skin eruptions was 27.3 years (range: 17–48 years) and the mean duration of the skin eruptions was 8.2 months (range: 2–18 months). The majority of the patients (60%) were asymptomatic but 26.7% complained of mild pruritus. Two-thirds of the patients had typical brown macules in confluent and reticulate pattern [Figure 2a and 2b] but 26.7% patients had scattered scaly brown macules and plaques. Shiny atrophic macules with scales were noted in two patients [Figure 3]. One patient had a non-pigmented lesion over chest and back covered with fine white scales [Figure 4] and two cases had verrucous lesions covered with dark scales [Figure 5]. The majority had lesions distributed over neck and upper trunk and many had lesions at multiple sites [Figures 6a and 6b, 7, 8a and 8b, 9]. KOH mount was done in 24 cases and was positive in three cases (12.5%). Biopsy was performed in nine patients including few patients with atypical morphology lesions, of which demonstrated variable degrees of hyperkeratosis, papillomatosis, and

Table 1: Clinical data of the patients (n=30)

| Symptoms                        | No. of patients (%) |
|---------------------------------|---------------------|
| Pruritus                        | 08 (27.7)           |
| Asymptomatic                    | 18 (60)             |
| Not documented                  | 04 (13.3)           |
| Distribution                    |                     |
| Face                            | 03 (10)             |
| Retroauricular area              | 04 (13.3)           |
| Neck                            | 18 (60)             |
| Upper trunk (Chest, shoulders, and back) | 20 (66.7) |
| Axillae                         | 02 (6.7)            |
| Lower trunk (Lower back and abdomen) | 06 (20) |
| Lesion pattern                  |                     |
| Scaly brown macules and plaques | 08 (26.7)           |
| Shiny atrophic macules          | 02 (6.7)            |
| Verrucous lesion with pigmented scales | 02 (6.7) |
| Nonpigmented with fine white scales | 01 (3.3) |
| Confluent, reticulate brown macules | 17 (56.7) |

Figure 1: Methodology of study

Figure 2: (a) Typical brown macules on chest with lesions confluent in the center and reticulate pattern at the periphery. (b) Typical brown macules in reticulate pattern on back

Figure 3: CRP lesions showing shiny atrophic macules with fine scales on the back
moderate acanthosis [Figure 10a and 10b]. Mild superficial inflammatory infiltrate is seen in one-third of the cases. Dermoscopy (Nonpolarized mode, DermLite DL4, California USA, 10X) observation was noted in eight cases that revealed thick brownish gyri and sulci indicating papillomatosis, focal white areas vasodilation with collagen, pinkish white areas against brown background. [Figure 11]. Five out of thirty patients had hypothyroidism and two among them had extensive lesions. Acanthosis nigricans was observed in nine patients who were obese as well. Prior treatment history is summarized in Table 2. Prior treatment with topical alone or combination of oral and topical therapy was taken by 28 (93.3%) patients. The majority of patients provided prior history of treatment with antifungals, either topical, oral, or both for 1–2 months without clearance. The response to the treatment is summarized in Table 3. Eighteen patients had received 100 mg minocycline once daily and eight were prescribed doxycycline 100 mg once daily (due to economic constraints) while four were prescribed azithromycin 500mg once daily for three weeks. But, 6e patients receiving doxycycline or azithromycin for three weeks without any
response were treated with minocycline 100mg OD for another three weeks. Thirteen (72.2\%) out of 18 patients on minocycline showed complete clearance within three weeks [Figure 12a and 12b] and three patients (16.6\%) had more than 50\% improvement at the end of three weeks. The latter group was continued on minocycline for another three weeks. Only two patients had less than satisfactory response. Four patients (22.2\%) reported recurrence within 6 months of stopping the medications. They were restarted on a two-week course of minocycline, followed by a four-weekcourse of doxycycline. The response of the patients who were treated with doxycycline (37.5\% had complete clearance) was much less robust. No major clinical adverse effect was noted during therapy. Those who reported with recurrence or those who did not respond to doxycycline were treated with minocycline 100mg OD for three weeks. Only 50\% of patients on azithromycin showed clearance of the lesions. No topical medications were prescribed.

### Discussion

Confluent and reticulate papillomatosis is an uncommon disorder, which is usually reported as case reports or small case series. This is the first largest cohort of CRP reported in India. The etiology of CRP is still not defined. Suggested etiological factors are keratinization disorder, genetic factor, endocrine abnormalities, reaction to *Pityrosporum*, reaction to UV light, and variation of cutaneous amyloidosis.\[14\] Earlier studies reported only the presence of yeast form of *M. furfur*, implying it to be a coincidental nonpathogenic coloniser. Few studies now have reported the presence of both yeast and hyphal forms in CRP, hypothesizing the abnormal keratinization as a response to *M. furfur*.\[7,8\] An inappropriate expression of keratin 16 in the stratum granulosum with an increase in transitional cell number has been documented in one report, reflecting aberrant keratinization.\[9\] It is speculated that in CRP, the improper keratinization may become self-perpetuating, making treatment with oral and topical antifungals ineffective.\[2\]

The baseline characters in the index study are consistent with other case series where the age of onset is mainly in young adults.\[10\] Tamraz *et al.* reported the age of onset to

### Table 2: Past treatment history

| Drug                  | No. of patients (%) |
|-----------------------|---------------------|
| Oral antifungal       | 14 (46.7)           |
| Fluconazole           | 11 (36.7)           |
| Ketoconazole          | 1 (3.3)             |
| Itraconazole          | 2 (6.7)             |
| Topical antifungal    | 17 (56.7)           |
| Clotrimazole          | 12 (40)             |
| Ketoconazole          | 2 (6.7)             |
| Miconazole            | 2 (6.7)             |
| Selenium sulfide      | 1 (3.3)             |
| Others topical        | 4 (13.3)            |
| Topical retinoids     | 1 (3.3)             |
| Steroids              | 1 (3.3)             |
| Combinations          | 2 (6.7)             |
Table 3: Response to treatment

| Drug          | No. of Pts (%) | Response (%) | Recurrence (%) | Retreatment done in patient with recurrence |
|---------------|----------------|--------------|----------------|--------------------------------------------|
|               |                | <50%         | 51%-90%        | >90% or complete clearance                 |
| Minocycline   | 18 (60.0)      | 2 (11.1)     | 3 (16.7)       | 13 (72.2)                                  | Minocycline followed by doxycycline 2 patients multiple recurrence |
| Doxycycline   | 8 (27.7)       | 1 (12.5)     | 4 (50.0)       | 3 (37.5)                                   | Switched to minocycline Complete clearance |
| Azithromycin  | 4 (12.3)       | 1 (25.0)     | 1 (25.0)       | 2 (50.0)                                   | Switched to minocycline Complete clearance |

Figure 12: (a) Pretreatment lesion of CRO on the chest. (b) Six-week post treatment with 100mg minocycline showing clearance of lesions

be in teens, post puberty, with most patients presenting in the early adult life. The average age of patients in our study was 27 years.

Stein et al. published a study of three siblings with CRP raising the possibility of a genetic predisposition. There was no family history in any of our patients. There was a higher predilection among females in this study. Most other studies showed male preponderance.

Most patients had the lesions for more than 8 months before presenting to our OPD. Though most case reports have reported this condition to be asymptomatic, 26.6% of patients in this case series complained of mild to moderate pruritus.

The distribution of the lesions in the present study was consistent with the most other reported studies. Confluent reticulate papules and macules were seen over the upper trunk in the majority of the patients. Only two patients had the involvement of the axilla in the present study which is in contrast to the other studies which described axilla as most frequently site. The involvement of the face and retroauricular area observed in the present study is an uncommon finding in comparison to the other studies.

The morphology of the lesions was that of classical brown macules in confluent and reticulate pattern in most of the cases (56.7%), whereas 26.7% patients had scattered lesions. Shiny atrophic macules with scales were noted in two patients (6.7%). Scrapings for KOH mount were done in 24 patients, but were positive in only three cases (12.5%), who demonstrated scaly macules clinically and hyphae without yeast forms under microscopy. These patients were first treated with antifungals for 1 month without any improvement in the lesions. This goes against the previous reports where CRP with positive KOH mount showed good response to antifungals. KOH mount was negative among the patients who complained of pruritus. Histopathology showed hyperkeratosis, acanthosis, and papillomatosis. Two patients showed with follicular plugging. The main histopathology findings are similar to acanthosis nigricans but the presence of lymphatic infiltrate around the dilated superficial blood vessels along with the beading of the elastic fibers was helpful diagnostic clue which was noted in three patients (33.3%) in the present study.

CRP has been reported to occur frequently in patients with endocrine abnormalities, such as diabetes mellitus and thyroid disease, especially with hyperthyroidism. In our study, five patients (16.7%) had hypothyroidism, and two of them had very extensive lesions. Association of hypothyroidism with CRP is a unique finding in the present study. Though this finding is not significant, the causal relations are not studied. The one possible explanation for this finding is the presence of obesity in hypothyroidism with in associated with CRP.

Common clinical and histopathology differentials [Table 4] are pityriasis versicolor, acanthosis nigricans, pseudoacanthosis nigricans, macular amyloidosis, Darier disease, pigmented contact dermatitis, lichen pigmentosus, dermatopathia pigmentosa reticularis, dyskeratosis congenita, flat warts, mycosis fungoides, and pityriasis rubra pilaris. A diagnosis of CRP is made by distinct findings of reticulate pattern without any associated abnormalities, negative fungal tests, histopathology of papillomatosis without florid inflammatory cell infiltrate, and a good clinical response to therapy with minocycline or azithromycin in most cases. None of the patients received oral retinoids in the present study.

Treatment of CRP remains a challenge. In 1965, Carteaudescribed the successful treatment of CRP with minocycline, the first such report. Since then, many reports have noted that minocycline is an effective treatment for CRP. It is believed that the antibiotics influence CRP positively through their antiinflammatory (most probably attributed to inhibiting neutrophil migration and subsequent
Table 4: Common differential diagnosis of CRP

| Etiopathogenesis | CRP | AN | TV | DD |
|------------------|-----|----|----|----|
| Etiopathogenesis | Exact etiology is unknown but many causes are postulated | Commonly associated with insulin resistance leading to increased production of insulin-like growth factors which can induce epidermal proliferation | Abnormal and delayed keratinization | Superficial fungal infection caused by *Malassezia* spp. | Autosomal dominant inherited disease due to mutation in *ATP2A2* gene |
| Age | Any age | Any age | Children, adolescents | Young adults | 15-30 years |
| Distribution | Upper trunk and axillae | Folds and creases-axilla, neck, cubital fossa, and groins | Neck, ankle, face | Seborrheic areas | Seborrheic areas |
| Morphology | Persistent, reticulate hyperpigmentation | Velvety hyperpigmented plaques, associated with increased skin markings | Dirt-like brown plaques | Macules with fine scaling | Greasy, crusted, keratotic, yellow-brown warty papules and plaques. Associated with V-shaped nicks at the edge of the nail and unpleasant odor. |
| Diagnosis | Mainly clinical. HPE shows undulating basket-weave hyperkeratosis, papillomatosis, focal acanthosis limited to the areas of rete ridge elongation, increased basal melanin pigmentation along superficial perivascular lymphocytic infiltrate around mildly dilated blood vessels | Mainly clinical. HPE shows papillomatosis, hyperkeratosis with minimal hyperpigmentation. Upward projection dermal papillae with thinning of the epidermis and absence of dermal inflammatory infiltrate. | Wiping with isopropyl alcohol will clear the lesion but not with soap and water. HPE shows compact orthokeratoses, hypermelanosis, with absent inflammation | Mainly clinical confirmed by KOH and culture | HPE shows acantholytic dyskeratoses with suprabasal clefts, corps rond and grains, superficial perivascular lymphocytic infiltrate. |
| Treatment | Topical retinoids, other keratolytics, Systemic minocycline | Treat underlying cause. Cosmetic improvement can be obtained by topical keratolytics | Cleaning with isopropyl alcohol | Topical &/or systemic antifungals | Systemic retinoids and doxycycline |

CRP: Confluent and reticulate papillomatosis. AN: acanthosis nigricans TFFD: Terra-firma-forme dermatosis PV: Pityriasis versicolor DD: Darier’s disease

reactive oxygen species release) rather than antibacterial action, since no bacterial trigger has been ever identified in CRP lesions.[16]

In our study, the patients showed good response to minocycline within 3 to 6 weeks. Only 22.2% out of 18 patients had recurrence within 6 months who recurred with same morphological lesion with fewer lesions. These recurrences responded to minocycline. The response of the patients who were treated with doxycycline was much inferior. Only 50% patients on azithromycin showed the clearance of lesions. Patient who had less response at the end of three weeks were given minocycline which cleared the lesions proving superiority of the minocycline over the others. But azithromycin can be a safe alternative in pregnant with CRP.

Supporting the concept that CRP is a disease of keratinization, retinoids have been shown to effectively treat CRP. The effectiveness of oral retinoids is mainly attributed to their antiinflammatory properties and their ability to normalize epidermal keratinization, proven to be defective in CRP.[17] Retinoid can be considered but not considered in the present study.

**Conclusion**

Confluent reticulate papillomatosis is an uncommon disease with profound psychological implication because of pigment abnormalities over the seborrheic areas. This condition has chronic course with recurrence and mimics many conditions leading to delay in diagnosis causing embarrassment to the patient. Dermatologists need to be an extra vigilant while dealing with such pigmentary abnormalities over seborrheic areas, especially when it is resistant to standard antifungal therapy to consider CRP as a diagnosis.
Limitation

Limitations of the study included the retrospective design. The histopathology and dermatoscopy were not done in all cases. Fungal and bacterial culture would have added to give more insight into the etiology.

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Conflicts of interest

There are no conflicts of interest.

References

1. Gougerot H, Carteaud A. Papillomatosepigmenteeinnominee. Bull Soc Fr Dermatol Syphiligr1927;34:719.
2. Tamraz H, Raffoul M, Kurbani M, KibbiAG, Abbas O. Confluent and reticulated papillomatosis: Clinical and histopathological study of 10 cases from Lebanon. J Eur Acad Dermatol Venereol 2013;27:e119-23.
3. Yesudian P, Kamalam S, Razack A. Confluent and reticulated papillomatosis (Gougerot–Carteaud): An abnormal host reaction to Malassezia furfur. Acta Derm Venereol (Stockh) 1973;53:381-4.
4. Scheinfeld N. Confluent and reticulated papillomatosis: A review of the literature. Am J Clin Dermatol 2006;7:305-13.
5. Davis MD, Weenig RH, Camilleri MJ. Confluent and reticulate papillomatosis (Gougerot-Carteaud syndrome): A minocycline-responsive dermatosis without evidence for yeast in pathogenesis. A study of 39 patients and a proposal of diagnostic criteria. Br J Dermato l2006;154:287-93.
6. Cannavo SP, Guarneri C, Borgia F, Guarneri B. Confluent and reticulated papillomatosis and acanthosis nigricans in an obese girl: Two distinct pathologies with a common pathogenetic pathway or a unique entity dependent on insulin resistance? J Eur Acad Dermatol Venereol 2006;20:478-80.
7. Nordby CA, Mitchell AJ. Confluent and reticulated papillomatosis responsive to selenium sulfide. Int J Dermatol 1986;25:194-9.
8. Hamaguchi T, Nagase M, Higuchi R, Takuchi I. A case of confluent and reticulated papillomatosis responsive to ketoconazole cream. Nippon Ishinkin Gakkai Zasshi 2002;43:95-8.
9. Jimbow M, Talpash O, Jimbow K. Confluent and reticulated papillomatosis: Clinical, light, and electron microscopic studies. Int J Dermatol 1992;31:480-3.
10. Becker KA, Schwartz RA. Confluent and reticulated papillomatosis. eMedicine Dermatology [journal serial online]. 2005. Available from: http://www.emedicine.com/derm/topic82.htm.
11. Stein JA, Shin HT, Chang MW. Confluent and reticulated papillomatosis associated with tinea versicolor in three siblings. Pediatr Dermatol 2005;22:331-3.
12. Sau P, Lupton GP. Reticulated truncal pigmentation: Confluent and reticulated papillomatosis of Gougerot and Carteaud. Arch Dermatol 1988;124:1272-1275.
13. El-Tonsy MH, El-Benhawi MO, Mehregan AH. Confluent and reticulated papillomatosis. J Am Acad Dermatol 1987;16:893-4.
14. Abbud Neto S, di Stasi LL, Pires MC, Coletta EN. Pseudo-atrophodermacolli and Gougerot-Carteaud confluent reticulated papillomatosis (shining atrophy). Med Cutan Ibero Lat Am 1987;15:477-80.
15. Chang SN, Kim SC, Lee SH, Lee WS. Minocycline treatment for confluent and reticulated papillomatosis. Cutis 1996;57:454-7.
16. Sassolas B, Plantin P, Guillot G. Confluent and reticulated papillomatosis: Treatment with minocycline. J Am Acad Dermatol 1992;26:501-2.
17. Lee MP, Stiller MJ, McClain SA, Shupack JL, Cohen DE. Confluent and reticulated papillomatosis: Response to high-dose oral isotretinoin therapy and reassessment of epidemiologic data. J Am Acad Dermatol 1994;31:327-31.