Lymphocytic infiltrate; Papillary dermis

India and the Middle East [3,4]. In 2001, Pock et al. [1] described seven of hyper pigmented, dark-brown maculae and patches in sun exposed (Figures 1 and 2).

except for one that showed a complete resolution. After a follow up of treated with topical steroids without any significant improvement keratinocytes of the basal epidermal layers. Only three patients were and granzyme positive lymphocytes in close contact with damaged Melanophages in the upper dermis were present in all cases. In case observed in all patients, but only in four patients were prominent. Moderate inflammatory infiltrate in the upper dermis with a band-like lymphocytic infiltrate in the upper dermis and melanophages in the papillary dermis. LPP inversus is a rare variant of LPP appearing in non-sun exposed areas. In contrast to LPP which occurs almost exclusively in dark skinned individuals, a comprehensive review of the literature revealed that about half of the cases reported of LPP inversus affects fair skinned individuals including Caucasian patients.

Keywords: Lichen planus pigmentosus; Hyper pigmented; Lymphocytic infiltrate; Papillary dermis

Introduction

Lichen Planus Pigmentosus (LPP) inversus is a rare variant of LPP occurring in flexural regions with asymptomatic to mildly pruritic violaceous and dark-brownish macules and/or patches [1]. Usually mucosae, scalp and palmoplantar area are not affected [2]. LPP is described almost exclusively in dark skinned individuals. We report here nine cases of LPP inversus in nine Caucasian patients, and an accurate review of the literature about the published cases. Including ours, 48 cases of LPP inversus have been reported, a half of which in Caucasian individuals.

Case Report

Nine Caucasian patients, five women and four men, with asymptomatic to mildly pruritic, sharply demarcated violaceous and hyperpigmented macules and patches located at different folds, mainly axillae and groins, were included in the study. Clinical and histopathological characteristics are shown on (Table 1). The age of onset of our patients range from 29-77 years, with a mean age of 44.7 years and a female:male ratio of 1.25:1. No association with systemic diseases, viral hepatitis and drug exposure was documented in any case. Lesions appeared from 4-18 months before diagnosis. A 4 mm punch biopsy was performed in all patients except patients 3 and 5. Histological changes were similar in all cases with a slight to moderate inflammatory infiltrate in the upper dermis with a band like pattern. Vascular alterations of the basal epidermal layers were observed in all patients, but only in four patients were prominent. Melanophages in the upper dermis were present in all cases. In case n. 8, immunohistochemistry showed the presence of CD8 positive and granzyme positive lymphocytes in close contact with damaged keratinocytes of the basal epidermal layers. Only three patients were treated with topical steroids without any significant improvement except for one that showed a complete resolution. After a follow up of 6-24 months, most patients showed persistent asymptomatic lesions (Figures 1 and 2).

Discussion

LPP is a rare lichenoid dermatitis characterized by the presence of hyper pigmented, dark-brown macules and patches in sun exposed areas occurring mainly in dark skinned individuals such as those from India and the Middle East [3,4]. In 2001, Pock et al. [1] described seven

| Patients  | Age | Sex | Location | Pruritus | Duration | Histology | Race |
|----------|-----|-----|----------|----------|----------|-----------|------|
| 1        | 46  | F   | axillae  | no       | 3 months | A,B,D     | caucasian |
| 2        | 29  | M   | axillae, groin | yes | / | A,C,D | caucasian |
| 3        | 76  | M   | axillae, yes | 8 months | / | caucasian |
| 4        | 75  | F   | intergluteal fold | no | 5 months | A,C | caucasian |
| 5        | 39  | F   | submammary, groin, axillae | no | 1 year | / | caucasian |
| 6        | 49  | M   | axillae, groin | no | >1 year | A,B | caucasian |
| 7        | 51  | M   | axillae, groin, popliteal folds | no | 4 months | C,D | caucasian |
| 8        | 37  | F   | genital area | no | / | A,C | caucasian |
| 9        | 77  | F   | axillae, groin | no | 4 months | A,B,D | caucasian |

A: Incontinence of pigment, B: Slight inflammatory infiltrates with lymphocytes in the upper dermis, C: Moderate inflammatory infiltrates with lymphocytes in the upper dermis, D: Hydropic degeneration of the basal layer of epidermis, E: Intensive lichenoid inflammatory reaction.

Table 1. Summary of clinical and histological data in our series of patients with LPP-inversus.

European Caucasian patients with lesions unrelated to sun exposure arising on intertriginous areas and proposed the term LPP inversus [1]. A comprehensive PubMed search (2001 - 30 March 2015) revealed additional 32 cases of LPP inversus described since (Table 2). Including our patients, of all the reported cases of LPP inversus about half (23/48) occurred in Caucasian individuals. The disease appears slightly more common in females (29 females vs 19 males) and the age ranges from 15 to 84 years, with a mean age at diagnosis of 54.2 years. About 80% of patients had lesions at the axillae, usually bilaterally, 50% at the groins and 23% in the submammary folds. One case with lesions in the post auricular sulci was reported [5]. The majority of patients had no or very mild pruritus, a factor that may contribute to a delay in physician consultation, and may cause an underdiagnosis of this disorder. The main differential diagnoses are erythema dyschromicum perstans

*Corresponding author: Anna Cagalli, Department of Medicine, Section of Dermatology, University of Verona, Italy, Tel: +39-045-8122547; Fax: +39-045-8122547; E-mail: anna@cagalli.it

Received February 02, 2016; Accepted March 09, 2016; Published March 14, 2016

Citation: Cagalli A, Colato C, Schena D, Girolomoni G (2016) Pigmented Papules and Patches of the Folds: A Case Series of Lichen Planus Pigmentosus Inversus with Review of the Literature. J Clin Case Rep 6: 732. doi:10.4172/2165-7920.1000732

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**Figure 1:** Clinical appearance of Lichen planus pigmentosus inversus: multiple hyperpigmented lesions with smooth surface. (A, B) Early erythematous-violaceous lesions at sacral area (A) and left axillary fold (B). (C) Sub-mammary and (D) axillary fold lesions resulting with the appearance of the late phase (brownish).

**Figure 2:** Histologic aspects of lichen planus pigmentosus inversus: basal vacuolar changes, a band-like infiltrate of lymphocytes in the upper dermis and incontinence of pigment (A). Numerous CD8+ cells in the basal epidermal layers (B), granzyme +cells in close apposition to damaged basal keratinocytes (C).

| References          | Age | Sex | Location                        | Pruritus | Duration | Histology | Race     |
|---------------------|-----|-----|---------------------------------|----------|----------|-----------|----------|
| Pock et al. 2001    | 66  | M   | axillae, back                   | mild     | 2 months | A,B       | caucasian|
|                     | 54  | F   | axillae, shins                  | /        | 6 months | A,B       | caucasian|
| 68 F                |     |     | axillae, groin, submammary      | /        | 5 months | A,B       | caucasian|
| 71 F                |     |     | axillae, groin                   | /        | 5 weeks  | A,D,E     | caucasian|
| 60 F                |     |     | axillae, groin                   | /        | 1 year   | A,C       | caucasian|
| 57 M                |     | M   | axillae, groin, wrists           | /        | 6 months | A,B       | caucasian|
| Munoz-Perez et al. 2002 | 27 | M   | axillae, abdominal fold, groin, upper limb | no | 2 months | A,D,E     | hispanic|
| Kashima et al. 2007 | 51  | F   | axillae, popliteal fold         | no       | 2 months | A,C,D     | asian     |
| 62 M                |     |     | axillae, popliteal fold, groin  | no       | 6 months | A,C,D     | asian     |
| Bennassar et al. 2009 | 84 | M   | axillae, neck                   | mild     | 2 months | D,E       | caucasian|
| 72 F                |     |     | inframammary                    | no       | 3 months | A,D,E     | caucasian|
| 59 M                |     | M   | axillae, groin                   | no       | several months | E | caucasian|
| 54 F                |     | F   | axillae, popliteal fold         | no       | 1 year   | A,C       | caucasian|
| Kim et al. 2007     | 70  | M   | groin                           | no       | 5 months | A,C,D     | asian     |
| Kim et al. 2008     | 49  | F   | groin                           | no       | several months | A,E   | asian     |
| 25 F                |     | F   | axillae                         | no       | 1 year   | A,D,E     | asian     |
| Ohishima et al. 2011 | 54 | F   | axillae, groin, submammary, neck, popliteal folds | mild | 4 months | A,B       | asian     |
| Jung et al. 2011    | 31  | F   | axillae, popliteal folds, antecubital folds | no | 5 years  | A,B       | asian     |
A: Incontinence of pigment. B: Slight inflammatory infiltrates with lymphocytes in the upper dermis. C: Moderate inflammatory infiltrates with lymphocytes in the upper dermis and absence of epidermic hyperplasia. There is an exuberant dermal fibroplasia, with no time for compensatory increased proliferation of keratinocytes, with no time for compensatory increased proliferation of keratinocytes. The pathogenesis appears to be related to a CD8+ T lymphocyte-mediated cytotoxic activity against basal keratinocytes.  

LPP inversus belongs to the lichenoid dermatosis which includes lichen planus, LPP, lichenoid drug eruptions, annular lichenoid dermatitis of youth, graft versus host diseases [7]. LPP inversus microscopically resembles late phase lichen planus lesions, with epidermic atrophy, irregular hydropic degeneration of the basal layer and absence of epidermic hyperplasia. There is an exuberant pigmented incontinence and a lichenoid inflammatory infiltrate with lymphocytes and histiocytes [2]. The pathogenesis appears to be related to a CD8+ T lymphocyte-mediated cytotoxic activity against basal keratinocytes [2] as suggested by immunohistochemical features performed in some patients, including our [3,8,9]. Pock et al. proposed that in LPP inversus the lichenoid reaction occurs within a short period of time with dramatically intensive hydropic degeneration of basal keratinocytes, with no time for compensatory increased proliferation of keratinocytes, as it occurs in typical lichen planus such that the papules transform quickly into brown macules [1,10]. No drugs, infections or systemic co-morbidities have been documented in LPP inversus cases neither in literature nor in our cases. External stimuli, such as friction [Koebner phenomenon], may be a triggering factor [9], but this has been postulated as an explanation for the isolated or exclusive distribution of lesions in intertriginous area [11], and it has not been confirmed.

Treatment of LPP-inversus is not well established. Some cases undergo spontaneous remission within months to years [2]. Topical treatment with high potency corticosteroids [9,12,13] or topical tacrolimus have been used to accelerate the process [12,14], but with minimal improvement. A case report showed only a slight lightening of the lesion after oral deflazacort 45 mg tapered gradually over a period of 2 months [15], and two cases reported improvement of lesions after the discontinuation of wearing tight underclothes [13]. Three of our cases were treated with topical steroids, with no significant improvement except for one that showed a complete resolution, five patients were lost at follow up and the last one had no treatment with spontaneous resolution of pruritus but permanence of pigmentation [16,17].

References

| Author(s) | Year | Patients | Location | Duration | Outcome |
|-----------|------|----------|----------|----------|---------|
| Pock et al. | 2001 | 5 | unspecified | several weeks | improvement |
| Majima et al. | 2013 | 65 | groin, axillae | no | A,C,E, middle-easten |
| Barros et al. | 2013 | 25 | axillae, neck, popliteal folds, groin | mild | A,D, E, asian |
| Nijhawan et al. | 2013 | 47 | axillae, retroauricular folds, intergluteal fold | mild | A,E |
| Ghorbel et al. | 2014 | 74 | neck, axillae, submammary folds, groin | yes | A,B, middle-easten |
| 45 F | axilla, submammary | yes | 2 months | A,D, middle-easten |
| 61 M | axillae | no | 3 months | E,A,D, middle-easten |
| 67 F | axillae, submammary, groin | no | 1 year | C,A,D, middle-easten |
| 55 M | axillae, groin | slight | 3 months | C,A,D, middle-easten |
| Murzaku et al. | 2014 | 45 | axilla | mild | 2 years |
| Chen et al. | 2015 | 15 | abdomen, left neck, axillae, groin, inframammary | no | B, A, asian |
| 44 F | abdomen, waist,axillae, groin | no | 6 months | C,A, asian |
| 35 F | axillae, groin, inframammary areas, popliteal folds, antecubital fossae, inner wrists, abdomen | no | 10 months | C,A, asian |

For those patients with more widespread lesions, post-inflammatory hyperpigmentation, figure erythema, fixed drug eruption and LPP [2]. The clinical and the histological features are usually sufficient in making the diagnosis. A case report described the dermoscopic features of LPP inversus, with diffuse brown patches containing multiple granular gray-brown dots and an overlying scale [6].

A: Incontinence of pigment. B: Slight inflammatory infiltrates with lymphocytes in the upper dermis. C: Moderate inflammatory infiltrates with lymphocytes in the upper dermis, D: hydropic degeneration of the basal layer of epidermis, E: Intensive lichenoid inflammatory reaction.

Table 2: Summary of LPP-inversus cases reported in literature.
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