Histopathological study of cutaneous non-neoplastic lesions in punch biopsies

Sakthidasan Chinnathambi P¹,*, Anitha Burra¹
¹Dept. of Pathology, ESIC Medical College, Hyderabad, Telangana, India

Abstract

Background: Skin being the largest organ of the body, is subjected to constant environmental insults through direct and indirect targets. Non-neoplastic lesions of skin comprise a vast array of diseases, which are usually approached by pattern based method in histopathology for microscopic diagnosis. This study was undertaken with an intention to learn such diseases by a simple minimally invasive punch biopsy procedure.

Materials and Methods: A 2 year retro-prospective study of 82 punch biopsies which were documented as non-neoplastic lesions of skin were studied with respect to their demographical and histopathological profile. Simple descriptive statistics was applied in Microsoft Excel software.

Results: Out of the 82 cases studied, 46 (56%) were males and 36 (44%) were females. Maximum number of cases (n=23) were seen in 21-30 years of age. Most prominent site of lesions biopsied were from lower limb (23 cases) with legs being the commonest among them. Cutaneous infections (n=25) was the most common clinical category, with Mycobacterial lesions as the prominent subcategory (n=16). Granulomatous reaction constituted the most common major tissue reaction pattern among other patterns with a total number of 17 cases out of 82. Panniculitis was the most common minor reaction pattern observed.

Conclusion: The pattern based approach in routine histopathological analysis proves a valuable descriptive tool for reaching an accurate diagnosis in cutaneous non-neoplastic lesions.

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1. Introduction

Skin being the largest organ of the body, is subjected to constant environmental insults through various direct and indirect targets. This explains the vast number of diseases that can occur in skin and these cutaneous lesions can be categorized broadly as non-neoplastic and neoplastic diseases. By far, non-neoplastic lesions outweigh the number of neoplastic lesions in the practice of clinical dermatology. Due to the varied presentations of these non-neoplastic lesions, and the myriad of diseases categorized under them, it is understood that an expertise knowledge is required for an accurate diagnosis.¹–³ Hence this study was undertaken with an intention to learn various cutaneous non-neoplastic lesions which were submitted for histopathological analysis by a simple minimally invasive punch biopsy procedure.

2. Aims & Objectives

To describe the various non-neoplastic lesions of skin with respect to their demographical profile and to categorize them based on histopathological patterns.

3. Materials and Methods

A two year retro-prospective cross-sectional study was undertaken in a tertiary care medical college hospital from 1ˢᵗ of January 2018 till 31ˢᵗ of December 2019, in the Department of Pathology. Institutional ethical clearance was obtained prior to the commencement of the study. Patients with skin diseases which required histopathological diagnosis were subjected to a 4mm punch
biopsy procedure done at an outpatient setup in the
Department of Dermatology & Venereology. The tissues
obtained were fixed immediately in 10% formalin and
sent to the Department of Pathology for histopathological
analysis. Biopsies were processed routinely in an automated
tissue processing and embedding system. Sections were
cut at 3-4 micrometer thickness using a semi-automated
microtome and stained by routine Hematoxylin and Eosin
stain. Special stains were done when and where required.
Demographic parameters were obtained from the case
records. All punch biopsy specimens which were diagnosed
as non-neoplastic skin diseases of any age group were taken
as inclusion criteria. Those cases which were subjected
to non-punch biopsy procedures which even though had
a non-neoplastic pathology were excluded from the study.
Sample size of 82 cases were studied in a period of 2 years.
Simple descriptive statistics was applied after computing the
collected data in Microsoft Excel software.

4. Results

Out of the 82 cases studied, 46(56%) were males and
36(44%) were females, with a male to female ratio of 1.27:1.
(Figure 1a). Age wise distribution is represented in (Figure 1
b). Maximum number of cases (n=23) were seen in 21-30
years of age which corresponded to 28% of the total cases.
Youngest patient’s age was 5 years, while the oldest one was
69 years. Most prominent site of lesions biopsied were from
lower limb (23 cases) with legs being the commonest among
them (9 cases).

Cutaneous infections (n=25) was the most common
clinical category, with mycobacterial lesions as the
prominent subcategory (n=16). Out of these 16 cases, the
most prominent cases were of leprosy (n=10), with their
varied presentations in histology. Among these 10 cases,
7 cases were biopsied in young patients of 21-30 age
group, out of which 6 of these patients were males. The
M:F ratio of leprosy patients subjected to punch biopsies
was 7:3. Eight of ten cases showed granulomatous lesions
in histology, among which 6 cases were diagnosed as
Borderline Tuberculoid leprosy and 2 were categorized as
Tuberculoid leprosy. The other two out of ten leprosy cases
showed lepromatous pattern with diffuse infiltrate of foamy
macrophages. Acid fast bacilli were noted in 8 out of 10
cases of leprosy.

Out of 25 cases of cutaneous infections, eight cases
were due to viral infections, 7 of which manifested as
 verruocous proliferations, either as verrucous hyperplasia
or verruca vulgaris. Interestingly, 6 of those cases were
noted in males in varying age range, and 5 of such
cases occurred in foot/palms presenting clinically as
warty outgrowths. One case of verrucous hyperplasia
was observed in nose. Histopathologically all these cases
were observed to possess koilocytic keratinocytes and
 verruciform hyperkeratosis. One case of HIV infection
presented with multiple skin colored itchy papules with
central crusting was noted in upper limb of 35-year-old
male, which was diagnosed histopathologically as pruritic
 papular eruption. One case of cutaneous leishmaniasis was
noted as generalized erythematous papulonodular lesions
with shiny surface, histology of which showed leishmanial
organisms in macrophages.

There were 6 cases of Mycobacterium Tuberculod
infection, all were diagnosed histopathologically as Lupus
vulgaris. Face was most common site of occurrence of
Lupus vulgaris with 2 cases each in cheek, and nose,
one in paranasal skin, and one in upper limb. Clinically
these lesions were erythematous in nature with two cases
presenting as plaques with central clearance whereas
the other two cases presented as papulonodular lesions.
Histopathologically all these cases were composed of
granulomatous reaction pattern, which were confirmed
by Ziehl Neelson’s acid fast staining for Mycobacterial
organisms.

Out of 82 cases, 14 cases were clinically categorized
purely into papulo-squamous in nature, while 3 cases were
having mixed clinical patterns. Out of these 14 cases,
predominant spongiosis pattern was observed in 8 cases,
lichenoid pattern was noted in 5 cases, and a single case
of psoriasiform reaction pattern. Among the 8 cases with
 spongiosis, 3 cases had pityriasisiform spongiosis, with
 pityriasis rosea as the commonest disease among them.
Erythematous patches to nodules were the commonest
clinical presentation of pityriasis rosea Other 5 cases of
spongiosis were allergic contact dermatitis(n=1) and small
 plaque parapsoriasis (n=4). Five cases of lichenoid reaction
pattern were recorded, with classic lichen planus, lichen
planus pigmentosus, annular lichen planus, hypertrophic
lichen planus, and systemic lupus erythematosus each
contributing to one case each. Out of these 5 cases, former
4 cases were noted in 3rd decade and all of them had
 hyperpigmentation with itchy macules to plaques in their
clinical presentation, while latter one case of systemic lupus
erythematosus was noted in 2nd decade in a male patient
interestingly. One case of psoriasis was noted, clinically
presenting as generalized erythroderma in a 53-year-old
male patient, biopsy of which revealed classic features of
psoriasis such as regular elongation of rete pegs with micro-
 muro neutrophilic abscesses.

Three cases had a mixed pattern of presentation, as
lichenoid together with spongiotic patterns (Lichenoid
contact dermatitis, prurigo nodularis and prurigo simplex),
all of which had multiple lesions associated with itching
and hyperpigmented macules to nodules on clinical
presentation.

Of the 82 cases, 9 cases had predominantly vasculopathic
reaction pattern in histopathology, manifesting clinically
as cutaneous vasculitis. Some of the vasculitis biopsied
were hypersensitivity vasculitis (n=5), urticarial vasculitis

(n=2), small vessel vasculitis and chronic lymphocytic vasculitis (each n=1). All cases of hypersensitivity vasculitis were diagnosed to be leucocytoclastic vasculitis on histopathology, with 4 of them presenting as purpurae while one was presenting as petechiae clinically. Multiple erythematous and edematous papules/plaques was the most common presenting symptom of urticarial vasculitis. A case of pyoderma gangrenosum was noted in a 45-year-old male as multiple hyperpigmented crusted plaques in his forearm. Histopathologically it was evident to have lymphocytic vasculitis with focal epidermal necrosis.

Vesiculo bullous diseases constituted 7 out of 82 cases, 5 of which occurred in females, with M:F ratio of 5:2. Most commonly diagnosed vesiculobullous disease was happened to be epidermolysis bullosa, one in 12-year-old female and other in 55-year-old male patient. The former patient had an inherited history of epidermolysis bullosa, while the latter was an acquired disease. Bullous pemphigoid, pemphigus vulgaris and sub-corneal pustular dermatosis were other blistering diseases (each n=1) exhibiting sub-epidermal, supra-basal and sub-corneal bullae respectively on histopathology. Two cases of Genodermatoses were encountered, one case was having multiple itching papules, pustules and crusts in axilla of 45-year-old male patient, while the other case was having cystic swelling in the lower lip of 33-year-old female patient. Both of which were diagnosed to be hailey-hailey disease and darrrier’s disease respectively, by the presence of acantholytic cells in a dilapidated brick-wall pattern in the former while the latter had dyskeratosis with acantholysis, accompanied by corps ronds and grains.

Eight out of 82 cases had septal/lobular inflammation of the subcutaneous fat (histologically refers to panniculitis). All 6 cases out of 8 had predominantly septal distribution of inflammatory cells, while 2 cases had predominantly lobular inflammation. Clinically the former correlated to have erythema nodosum and latter, erythema induratum with nodular vasculitis. One of these cases of erythema nodosum had leprosy as clinical diagnosis, which was finally diagnosed to be erythema nodosum leprosum, after confirmation with acid fast stain for lepra bacilli. Exclusively all these cases of erythema occurred on limbs, especially on legs.

There were 7 cases of cutaneous appendageal disorders of which alopecia constituted the majority (n=6) in number. Out of these, idiopathic scarring alopecia (pseudo pelade of Brocq) consisted of 4 cases and non-scarring alopecia (alopecia areata) consisted of 2 cases. Most of these alopecias had common presentation of patchy hair loss and M:F ratio was found to be 1:2. The other appendageal disorder had erythematous follicular papules in skin of breast with discharge from the lesion, which was diagnosed histopathologically as Fox- Fordyce disease (Apocrine miliaria).

There were 9 cases of miscellaneous diseases, which included bowen’s disease (n=2), polymorphous light eruption (n=2), and single case of morphea, photodermatosis, lichenoid drug eruption, idiopathic macular eruptive hyperpigmentation and cutaneous lymphoid hyperplasia respectively.

Few cases of interest are depicted in the Figure 2 a-f.

Fig. 1: a: Distribution of cases with respect to gender; b: Distribution of cases with respect to Age.

Fig. 2: a: Hailey-Hailey disease, (acantholytic dyskeratosis with dilapidated brick wall pattern) (H&E; 40X); b: Darrrier’s Disease, (prominent corps ronds & grains) (H&E; 100X); c: Pemphigus vulgaris suprabasal clefting and acantholysis (H&E;100X); d: Leucocytoclastic vasculitis, (leucocytoclasis with neutrophils & extravasation of fibrin) (H&E 100X); e: Lupus Vulgaris (well-formed epithelioid cell granulomas in dermis) (H&E 100X); f: Cutaneous Leishmaniasis, (Leishmanial Organisms in histiocytes) (H&E 400X)

5. Discussion

The present study was retro-prospective one with a total number of cases accounting to 82 in a period of 2 years. In a study by Veldhurthy VS et al, the total number of cases studied were 92, while study by Reddy et al accounted to 80 cases.4,5 In a study by Singh et al a total of 112 cases were studied.6 The present study was conducted on 82 patients
Table 1: Categorization of Non-neoplastic diseases of skin with respect to broad clinical categories

| Broad Clinical Categories | Sub Categories |
|---------------------------|----------------|
| Cutaneous infections (n=25) | Bacterial Infections (n=17) Mycobacterium Lepra (n=10) Mycobacterium Tuberculosis (n=6) |
|                           | Viral Infections (n=8) HPV Related (n=7) |
|                           | Parasitic Infection (n=1) HIV Associated (n=1) |
|                           | Spongiotic disorders (n=8) Cutaneous Leishmaniasis (n=1) |
| Papulo-squamous disorders (n=16) | Lichenoid Dermatoses (n=4) Allergic Contact Dermatitis (n=1) |
|                           | Psoriasiform Reaction Pattern (n=1) Lichen Planus and its variants |
|                           | Mixed Reaction Pattern (n=3) Psoriasis Vulgaris |
|                           | Leucocytoclastic Vasculitis (n=5) |
|                           | Urticarial Vasculitis (n=2) |
|                           | Erythema Elevatum Diutinum (n=1) |
| Vasculitis (n=9) | Pyoderma Gangrenosum (n=1) |
|                           | Erythema Nodosum (n=5) |
| Panniculitis (n=8) | Septal Panniculitis (n=6) Erythema Nodosum Leprosum (n=1) |
|                           | Lobular Panniculitis (n=2) Erythema Induratum Nodular Vasculitis |
|                           | Subcorneal Bullous Disorder (n=1) Subcorneal Postular Dermatosis |
| Blistering Dermatoses (n=5) | Suprabasal Bulla (n=1) Pemphigus Vulgaris |
|                           | Subepidermal Bulla (n=3) Bullous Pemphigoid (n=1) |
|                           | Bowen’s Disease Epidermolysis Bullosa (n=2) |
| Premalignant disorders (n=2) | Hailey Hailey Disease (n=1) |
|                           | Darrier’s Disease (n=1) |
| Genodermatoses (n=2) | Alopecia (n=6) Scarring Alopecia (n=4) |
|                           | Apocrine miliaria (n=1) Non-Scarring Alopecia (n=2) |
| Appendageal disorders including Alopecia (n=7) | Autoimmune dermatoses (n=1) [Subacute Lupus Erythematosus] Fox – Fordyce’s Disease (n=1) |
|                           | Localized Connective tissue Disorder (n=1) [Morphea] |
|                           | Cutaneous Toxic Disorders (n=4) Polymorphous Light Eruption (n=2) |
|                           | Autoimmune dermatoises (n=1) [Subacute Lupus Erythematosus] Photodermatitis (n=1) |
| Autoimmune & connective tissue dermatoses (n=2) | Localized Connective tissue Disorder (n=1) [Morphea] |
|                           | Drug Toxicity (n=1) [Lichenoid Drug eruption] Photodermatitis (n=1) |
| Pigmentation Disorders (n=1) | Photodermatoses (n=3) |
|                           | Idiopathic Macular Eruptive Hyperpigmentation |
| Cutaneous infiltrates (n=1) | Cutaneous Lymphoid Hyperplasia |

which was in par with most of the above mentioned studies in the literature. Forty-six cases (56.09%) were males and thirty six (43.9%) were females with M:F ratio of 1.27:1. This was similar to study by Singh et al, where 61% of cases were males and Gupta et al where M:F ratio was 1.05:1. Considering age, present study shows maximum number of cases in 21-30 years of range (3rd decade, n=23 which accounted 28% of total number of cases), which was similar to Veldhurthy et al and Younas et al. Reddy et al & Gupta et al documented large number of cases in the 4th decade. Among the various sites, 23 cases fallen in the category of lower limbs with legs being the commonest of all. This was followed by upper limb, head and neck, multiple sites, trunk and perineum in the descending order respectively. This is in accordance with D’costa et al where lesions most commonly occurred in extremities. Considering the histopathological reaction pattern analysis, the most common major tissue reaction pattern was granulomatous in nature with a total of 17 cases, followed by spongiotic (n=8) vasculopathic (n=9) vesiculobullous (n=7) and lichenoid (n=5) respectively. In the study by Singh et al, granulomatous reactions constituted 2nd most common pattern analyzed, with 23.5% of cases, while in the study by Veldhurthy et al, 36.9% had lichenoid reactions which constituted the bulk of cases in them. In the study by Reddy et al, psoriasiform reactions constituted the maximum number of cases with 42.5% of cases followed by Lichen planus. The reason for decrease in number of
Table 2: Classification of diseases based on Major Tissue reaction patterns.

| Major Tissue Reaction Patterns [n=51] | Specific diseases | Number of Cases |
|--------------------------------------|-------------------|-----------------|
| Vesiculo-bullous Reaction Pattern [n=7] | Pemphigus Vulgaris | 1 |
|                                      | Subcorneal Pustular Dermatitis | 1 |
|                                      | Bullous Pemphigoid | 1 |
|                                      | Epidermolysis Bullosa | 2 |
|                                      | Hailey Hailey Disease | 1 |
|                                      | Darrier's Disease | 1 |
|                                      | Lupus Vulgaris | 6 |
| Granulomatous Reaction Pattern [n=17] | Lepromatous Leprosy | 2 |
|                                      | Tuberculoid Leprosy | 1 |
|                                      | Borderline Tuberculoid Leprosy | 7 |
|                                      | Cutaneous Leishmaniasis | 1 |
|                                      | Leucocytoclastic Vasculitis | 5 |
| Vasculopathic Reaction Pattern [n=9] | Pyoderma Gangrenosum | 1 |
|                                      | Erythema Elevatum Diutinum | 1 |
|                                      | Small Plaque Parapsoriasis | 4 |
|                                      | Pityriasis Rosea | 3 |
| Spongiotic Reaction Pattern [n=10] | Allergic Contact Dermatitis | 1 |
|                                      | Fox Fordyce’s Disease | 1 |
|                                      | Prurigo simplex | 1 |
|                                      | Classical Lichen Planus | 1 |
|                                      | Hypertrophic Lichen Planus | 1 |
|                                      | Annular Lichen Planus | 1 |
| Lichenoid Reaction Pattern [n=7] | Lichen Planus Pigmentosus | 1 |
|                                      | Lichenoid Contact Dermatitis | 1 |
|                                      | Lichenoid Drug Eruption | 1 |
|                                      | Subacute Lupus Erythematosus | 1 |
| Psoriasiform Reaction Pattern [n=1] | Psoriasis Vulgaris | 1 |

Table 3: Classification of diseases based on Minor reaction patterns

| Minor Reaction Patterns | Specific Diagnosis | Number of Cases |
|-------------------------|--------------------|-----------------|
| Panniculitides [n=8]    | Erythema Nodosum   | 5               |
|                         | Erythema Nodosum Leprosum | 1 |
|                         | Erythema Induratum Nodular Vasculitis | 2 |
| Verruciform (Church spire like) | Verruca Vulgaris | 4 |
| Hyperplasia of epidermis [n=7] | Verrucous Hyperplasia | 2 |
|                         | Verruca Plantaris | 1 |
|                         | Morphea | 1 |
| Dermal Infiltrates [n=2] | Cutaneous Lymphoid Hyperplasia | 1 |
| Hyperpigmentation [n=1] | Idiopathic Macular Eruptive Hyperpigmentation | 1 |
| Dysplasia [n=2]         | Bowen’s disease | 2 |
|                         | Alopecia Areata | 2 |
| Alopecias [n=6]         | Pseudopelade Of Brocq | 4 |
|                         | Pruritic Papular Eruption | 1 |
|                         | Prurigo Nodularis | 1 |
| Miscellaneous Diseases [n=5] | Polymorphous Light Eruption | 2 |
|                         | Photodermatitis | 1 |
biopsies of psoriasis and lichen planus compared to other studies is that, not all cases of clinically evident diagnosis were subjected to punch biopsy.

The presentation of large number of patients with infectious granulomatous reaction pattern may be attributed to the demographical and socio-economic status of Indian subcontinent, such as over-crowding, population explosion and improper hygiene in underdeveloped areas. Leprosy is still the most common cause of infectious granulomatous condition. Hypo-aesthesia is the prominent clinical symptom presented in 8 patients while the most common accompanying symptom was hypopigmentation. One case was presented with nerve thickening, which was identified to have an intra-neural granuloma on histology. Among individual cases, the maximum number of cases was shared by borderline Hansen’s (6 / 82) similar to Kumar et al and Lupus vulgaris (5/82), trailed by leucocytoclastic vasculitis (5/82). All those cases of lichenoid reaction pattern had either interface dermatitis or basal vacuolar change with inflammation as their histologic manifestations.

Among those less common diseases encountered, bowen’s disease had full thickness dysplasia of epithelium, both polymorphous light eruption and photodermatitis shared a common feature of phototoxic reaction to sunlight with subepidermal edema and vesiculation of epidermis along with inflammatory cells. Idiopathic macular eruptive hyperpigmentation had increased pigment in basal layer, pigmentary incontinence & perivascular lymphohistiocytic infiltrate.

6. Conclusion
Non–neoplastic lesions of skin include a vast array of disease categories and studying them in a methodical approach, like understanding the various histopathological reaction patterns and clinical categorizations with demographic profiles helps in arriving accurate diagnosis. Nevertheless, discussion with dermatologists is of utmost importance for understanding various clinical presentations of diseases with respect to specified tissue reaction patterns observed histopathologically and vice versa.

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8. Conflicts of Interest
There are no conflicts of interest.

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Author biography
Sakthidasan Chinnathambi P, Assistant Professor
Anitha Burra, Specialist Grade 2 (Senior)

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