Original Article

Clinico-epidemiology and Histological Spectrum of Nodular Skin Lesions: A Single-center Cross-sectional Study

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Abstract

Background: Nodular skin lesions are a common diagnostic dilemma because of overlapping clinical features. Histopathology remains the gold standard for diagnostic confirmation. **Aims and objectives:** The aim of this article is to analyze the clinico-epidemiology and histological spectrum of nodular skin lesions along with clinico-pathological correlation. **Materials and methods:** A cross-sectional study was conducted including 114 new patients with cutaneous nodules. Each patient was subjected to detailed clinical examination and histopathological examination to obtain the final diagnosis and degree of histomorphological concordance. **Results:** Neoplastic disorders accounted for 42.9% of the skin nodules among 114 patients (mean age 33.2 ± 11.9 years; M: F 1.7:1), followed by miscellaneous (30.7%), infective (19.3%), and deposition (7%) disorders. The most common cause was lipoma (19.3%), followed by prurigo nodularis (12.3%), leprosy (11.4%), and neurofibroma (9.6%). Most common site was trunk, and pruritus is the commonest symptom. Multiple clinical differentials were considered for almost one-third of patients owing to overlapping clinical features, and histology provided the final diagnosis. On clinico-pathological correlation, 72.8% of the cases showed histopathological concordance, whereas the remaining cases were histologically discordant (7%) or inconclusive (20.2%). **Conclusion:** Neoplastic disorders (benign> malignant) are the most common cause of nodular skin lesions. In addition to detailed clinical examination, histopathology is necessary to confirm the diagnosis and rule out differentials. Considerable histopathological correlation can be obtained for skin nodules if performed appropriately.

Keywords: Histopathological correlation, nodules, skin

Introduction

The type of primary skin lesion is essential for accurate clinical diagnosis, nodule being an important lesion.[1] Cutaneous nodular lesions represent a heterogeneous group, either reflecting a primary skin disease or underlying systemic involvement. Three primary categories of skin disorders may present with nodules: inflammatory or reactive, infectious, and neoplastic.[2]

Although most nodular skin disorders can be diagnosed clinically by history and detailed examination, some require additional histopathological evaluation for diagnostic confirmation. A definitive histomorphologic diagnosis is essential for these disorders, as treatment and prognosis vary accordingly.

However, literature is scarce regarding skin diseases specific to a basic lesion, especially nodules. Cutaneous nodular lesions have mostly been reported as isolated cases, whereas few publications exist concerning specific etiology of cutaneous nodules.[2-4] The current study was undertaken to evaluate the clinico-epidemiology and histomorphology of nodular skin lesions, along with clinico-pathological correlation.

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Materials And Methods

We conducted a cross-sectional study at the Department of Dermatology of a tertiary-care center across 15 months (January 2019 to March 2020) after obtaining requisite institutional approval. We enrolled consecutive patients presenting with skin nodules as their primary complaint, who provided written informed consent or assent and agreed to skin biopsy for histopathology. Acute pyogenic infections were excluded.

Each participant was subjected to detailed clinical history with emphasis on demographic parameters, duration of lesions, family history, and associated clinical symptoms such as fever and joint pain. Detailed dermatological examination was done to note the number, morphology, and site of lesions. General and systemic examination including lymph-node palpation was performed to rule out systemic involvement. Imaging (USG/CT scan/MRI) was undertaken when indicated, to exclude internal extension, whereas chest X-ray was performed routinely. We aimed to obtain a provisional diagnosis, but differentials were considered for overlapping clinical features. Routine biochemistry and HIV serology were done in all patients, whereas the venereal disease research laboratory test was done when necessary.

A representative skin nodule from each patient was subjected to skin biopsy and histopathology. All samples were stained with hematoxylin and eosin (H&E) and special stains (e.g., AFB, PAS, Giemsa) when indicated. Two blinded authors performed histopathological analysis to eliminate bias. Subsequently, clinico-pathological correlation was ascertained and noted. For analysis, we graded clinico-pathological correlation as: *Concordance*—histopathological diagnosis corroborated the clinical diagnosis, *Discordance*—histopathology inconsistent with clinical diagnosis, leading to revised diagnosis, and *Undecided*—histopathology did not reveal any specific diagnosis.

Statistical analysis

Data were entered in a Microsoft Excel spreadsheet and statistically analyzed using MedCalc® v12.5.0. We used mean and standard deviation for descriptive statistics and proportion/percentage for categorical data. Normal distribution of numerical variables was determined using the Shapiro–Wilk test. The χ^2 test was used for categorical data, whereas analysis of variance and Kruskal–Wallis test were applied for parametric and non-parametric data, respectively. A *P*-value <0.05 was considered significant.

Results

During the study period, 25,525 patients attended our outpatient department (OPD); among them, 121 were screened for cutaneous nodules and 114 finally enrolled after satisfying the eligibility criteria (the remaining 7 patients were excluded as they refused to undergo skin biopsy). So, the overall prevalence of cutaneous nodules was 0.47% (121/25,525).

The mean (SD) age of our patients (n = 114) was 33.2 (11.9) years, majority (69, 60.5%) belonging to the 20–39 year age group. We noted male preponderance (M:F 1.7:1). The disease duration ranged from 0.5 to 240 months [median 12 months, interquartile range (IQR) 3–36, 95% confidence interval 6.1–23.6]. Pain (33, 28.9%) and pruritus (24, 21.1%) were the predominant symptoms. We categorized our patients into four groups based on the final histological diagnosis: neoplastic (n = 49), infective (n = 22), deposition disorders (n = 8), and miscellaneous disorders (n = 35). These groups were statistically comparable with respect to age, sex, and family history ($P > 0.05$). Duration of disease was significantly low for infective disorders when compared with other groups ($P < 0.0001$, Kruskal–Wallis test with *post hoc* analysis) [Table 1].

Overall, lipoma (22, 19.3%) was the commonest cause of nodular skin lesions, followed by prurigo nodularis (14, 12.3%), leprosy (13, 11.4%), and neurofibroma (11, 9.6%) [n = 114].

Among neoplastic disorders (n = 49), lipoma (22, 44.9%) was followed by neurofibroma (11, 22.4%) and dermatofibroma (7, 14.3%) [Figure 1]. Two patients had non-Hodgkin's lymphoma (NHL) (one primary cutaneous anaplastic large cell lymphoma and one diffuse large B-cell lymphoma) and one patient keratoacanthoma, all three having palpable lymphadenopathy. Collagenoma (2) and one case each of basal cell carcinoma, schwannoma, poroma, and cutaneous leiomyoma [Figure 2], comprised the remainder. Among infective disorders (n = 22), leprosy predominated (13, 59.1%), followed by nodular scabies (6, 27.3%), whereas molluscum contagiosum and secondary syphilis accounted for two and one case, respectively. Leprous nodules comprised erythema nodosum leprosum (ENL) (10) [Figure 3], histoid leprosy (2), and lepromatous leprosy (1). Deposition disorders caused cutaneous nodules in only 8 (7%) patients, idiopathic scrotal calcinosis (6) being more frequent than xanthoma (2). Those diseases which could not be categorized comprised the miscellaneous disease group (n = 35), the causes being prurigo nodularis (14, 40%) [Figure 4], EN (7, 20%), granuloma pyogenicum (5, 14.3%), nodular acne (5, 14.3%), and sarcoidosis (2, 5.7%), whereas juvenile xanthogranuloma and Jessner's lymphocytic infiltrate accounted for one case each.

In our study, 114 patients presented with 252 nodular lesions in different anatomical sites, as most patients presented with multiple lesions. Most patients with neoplastic (11/49, 22.4%) and infective disorders (13/22, 59.1%) demonstrated >20 lesions. Maximum nodules [112/252 (44.4%)] were located in the trunk [back (48)>

Table 1: Clinico-demographic parameters (n = 114)

Parameters	Clinical category			
	Neoplastic (n=49)	Infective (n=22)	Deposition disorders (n=8)	Miscellaneous (n=35)
Age (in years)				
Mean (SD)	31.7 (11.5)	32.1 (11.2)	31.7 (7.4)	36.4 (13.7)
0–19 years	7 (14.3%)	3 (13.6%)	1 (12.5%)	3 (8.6%)
20–39 years	31 (63.3%)	13 (59.1%)	7 (87.5%)	18 (51.4%)
40–59 years	10 (20.4%)	6 (27.3%)	0 (0)	12 (34.3%)
≥60 years	1 (2%)	0 (0)	0 (0)	2 (5.7%)
Sex (M:F)	1.6:1	1.4:1	8:0	1.3:1
Duration of disease (in months)*				
Median	24	**2.5**	21	9
IQR	6.7–60	**1–5**	9.5–75	2–36
Family history				
Present	9 (18.4%)	4 (18.2%)	2 (25%)	1 (2.9%)
Absent	40 (81.6%)	18 (81.8%)	6 (75%)	34 (97.1%)
Pain				
Present	7 (14.3%)	11 (50%)	0 (0)	15 (42.9%)
Absent	42 (85.7%)	11 (50%)	8 (100%)	20 (57.1%)
Itching				
Present	0 (0)	6 (27.3%)	1 (12.5%)	17 (48.6%)
Absent	49 (100%)	16 (72.7%)	7 (87.5%)	18 (51.4%)

*P<0.05, K–W test with *post hoc* analysis

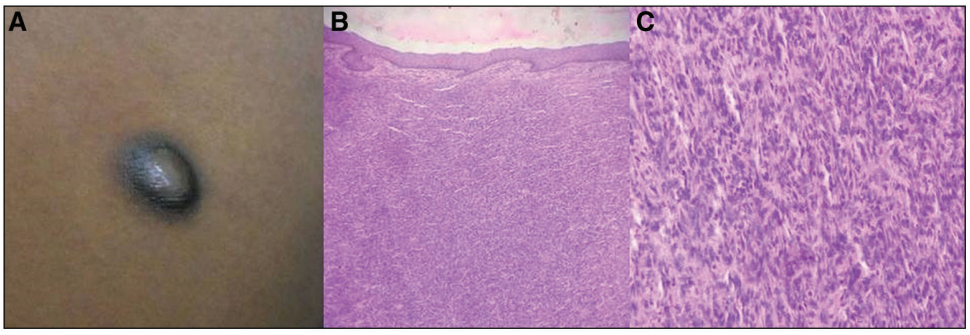

Figure 1: (a) Dermatofibroma, (b) epidermal hyperkeratosis and Grenz-zone (H&E, 100×), (c) spindled cells in storiform pattern (H&E, 400×)

abdomen (38) > chest (26)], followed by extremities [100/252 (39.7%); upper limbs > lower limbs]. Genitalia accounted for minimal nodules (13/252, 5.1%), whereas 27/252 (10.7%) cutaneous nodules were localized to the head-neck region. Leprosy (ENL) was the commonest cause of skin nodules in the head-neck region (37%) and chest (34.6%), followed by neurofibroma and nodular acne. Other notable causes included basal cell carcinoma, xanthoma, secondary syphilis (head and neck), molluscum contagiosum, lipoma, and granuloma pyogenicum (chest). Lipoma accounted for most abdominal nodules (39.5%) and back (35.4%), followed by neurofibroma and leprosy including reaction. Leprosy was the second most common cause of nodules over extremities following lipoma and prurigo nodularis in upper and lower limbs, respectively. Nodular scabies and idiopathic scrotal calcinosis accounted for six nodules each in the genitalia, along with a single case of juvenile xanthogranuloma.

We considered a single diagnosis in 78 (68.4%) patients, whereas multiple diagnoses were considered in rest due to overlapping clinical features and final diagnosis was established by histology. Regarding clinico-pathological correlation [Table 2], histological concordance was obtained in 83 (72.8%) patients (n = 114), whereas in 31 (27.2%) cases, histology was discordant or inconclusive (P = 0.1, χ^2). Maximum histological concordance was noted in neoplastic disorders (39/49, 79.6%), followed by miscellaneous disorders (27/35, 77.1%), infective group (13/22, 59.1%), and deposition disorders (4/8, 50%). In eight (7%) patients, the final diagnosis had to be changed from clinical suspicion due to histological discordance: Jessner's lymphocytic infiltrate (1) (clinically sarcoidosis), dermatofibroma (1) (clinically blue nevus), schwannoma (1) (clinically dermatofibroma), xanthoma (1), keratoacanthoma (1) (clinically cryptococcosis in both), prurigo nodularis (1) (clinically verrucous discoid

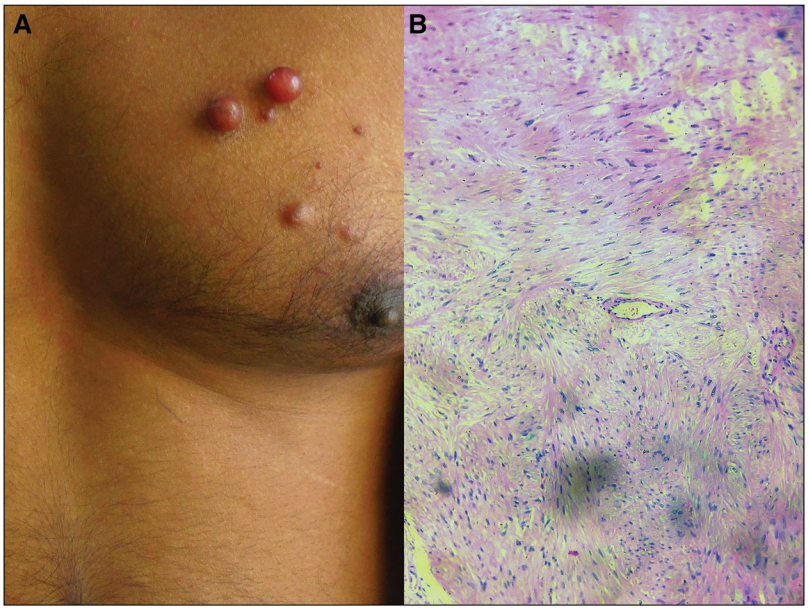

Figure 2: (a) Cutaneous leiomyoma, (b) fascicular arrangement of smooth muscle cells, fibrous stroma, vascular channel (center) (H&E, 100×)

Figure 3: ENL presenting as facial nodules

lupus erythematosus) and molluscum contagiosum (2) (clinically diagnosed as granuloma pyogenicum and pilomatricoma).

Discussion

Our exploratory study included 114 patients, majority belonging to the 20–39 years age group, mean (SD) age being 33.2 (11.9) years. Our findings are consistent with Adhikari *et al.*,[5] Bezbaruah and Baruah,[6] and Abubakar *et al.*[7] (clinico-pathological study of all morphological skin lesions), while our mean age is slightly less than that of Maharaja *et al.*[3] (37.4±12.7 years), who studied the clinico-pathological spectrum of inflammatory leg nodules exclusively, the latter being skewed toward adults usually suggestive of underlying systemic involvement.

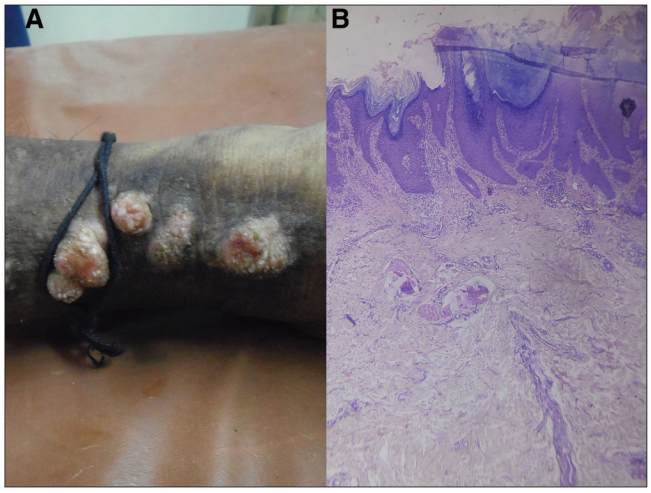

Figure 4: (a) Prurigo nodularis. (b) Epidermal orthokeratosis with irregular acanthosis, dermal infiltrate (H&E, 100×)

Our male preponderance is consistent with several authors,[3,5,8] whereas others have reported female predilection.[6,9] In the current study, median duration of the disease was 12 months, much more than that reported by Maharaja *et al.*[3] (5 months), possibly attributable to delayed presentation to dermatologists after exhausting all indigenous and local remedies.

We found trunk to be the commonest site for skin nodules in 44.4% of the cases, whereas Adhikari *et al*[5] and Bezbaruah and Baruah[6] found extremities (both upper and lower) and face to be maximally affected, respectively. Leg nodules were observed in 17.1% of the patients, most common etiology being prurigo nodularis, followed by ENL and EN. Maharaja *et al.*[3] reported EN to be the commonest cause of inflammatory leg nodules.

Table 2: Clinico-pathological correlation (n = 114)

Histopathological diagnosis	Clinical category			
	Neoplastic (n = 49)	Infective (n = 22)	Deposition disorders (n = 8)	Miscellaneous (n = 35)
Concordance (%)	39 (79.6)	13 (59.1)	4 (50)	27 (77.1)
Discordance (%)ǂ	3 (6.1); schwannoma (1), DF (1), KA (1)	2 (9.1); MC (2)	1 (12.5); xanthoma (1)	2 (5.7); prurigo nodularis (1), JLI (1)
Inconclusive (%)	7 (14.3)	7 (31.8)	3 (37.5)	6 (17.1)

ǂFinal diagnosis after histopathological correlation mentioned. DF = dermatofibroma, KA = keratoacanthoma, MC = molluscum contagiosum, JLL = Jessner's lymphocytic infiltrate

In our study, neoplastic disorders were the commonest cause of skin nodules in 43% of the subjects, much lower than that by Adhikari *et al.*[5] (19.7%); this may be explained as the latter included all skin lesions in addition to nodules. However, our finding is in agreement with Bezbaruah and Baruah[6] and Abubakar *et al.*[7] who observed neoplastic disorders to the commonest cause of skin nodules.

Lipoma was our commonest skin tumor in 44% of the cases. Tatar *et al.*[10] also reported lipoma to the commonest skin tumor (37.5%) in a cohort of Turkish patients, pain being the commonest symptom, similar to our study. We noted a single case of nodular basal cell carcinoma, while it was found to be the commonest cause of skin tumor, irrespective of morphology, in a study from Nepal.[5]

Dermatofibroma accounted for nodules in 14.3% of the patients, mostly located on lower extremities of females. Zaccaria *et al.*[11] also reported similar clinical profile for this tumor. One case of dermatofibroma was clinically reported as blue nevus, and histology helped us to arrive at the correct diagnosis, thus highlighting its vital role.

Interestingly, two patients with NHL presented with isolated skin nodules, finally diagnosed by histology (one primary cutaneous anaplastic large cell lymphoma and one diffuse large B-cell lymphoma). This is a rare presentation of NHL, as reported by Shen *et al.*,[12] in a case of diffuse large B-cell NHL.

In our study, prurigo nodularis was the second most common cause of cutaneous nodules in 12.3% of the patients, the commonest among miscellaneous disorders. A similar clinical profile was described by Kestner *et al.*[13] for this disease, who observed acquired perforating dermatoses to be the commonest clinical differential. EN was our second most common miscellaneous disorder and fifth among all disorders.

Infective disorders accounted for cutaneous nodules in 19.3% of the patients, leprosy (59%) being commonest followed by nodular scabies, molluscum contagiosum, and secondary syphilis. Overall leprosy caused cutaneous nodules in 11.4% of the patients. Among leprosy cases (13), 77% represented ENL, much higher when compared with that of Kumar *et al.*,[14] who recorded ENL in 4.8% of the patients. In our study, all ENL cases were of lepromatous pole, whereas in the later study,[14] 47.5% of the ENL cases were of lepromatous leprosy pole. We found biopsy-proven histoid leprosy in 15.4% of the cases, whereas Kalla *et al.*[15] found the same in only 2.8% of the leprosy patients. This discrepancy possibly occurred as we exclusively considered nodular presentation of leprosy which included only lepromatous cases, thus raising the incidence of histoid leprosy and ENL.

Regarding deposition diseases, idiopathic scrotal calcinosis caused skin nodules in three-fourth of the cases. Several Western authors have reported nodular cutaneous amyloidosis to be a notable cause[16,17]; however, we failed to find any patient with this deposition disorder. Joseph *et al.*[18] reported sebaceous cyst to be the commonest cause of scrotal nodule, whereas we found nodular scabies and idiopathic scrotal calcinosis to be the predominant causes of scrotal nodule (46% of the cases each).

We detected histopathological correlation/concordance in 72.8% of the patients, higher than that reported by Maharaja *et al.*[3] (33.3%, inflammatory leg nodules) and Agrawal *et al.*[19] (62%, papulosquamous lesions). This variation may be explained by exclusive inclusion of nodular skin lesions in our study, irrespective of site, after adequate clinical screening. However, our finding is comparable to Saha *et al.*,[20] who observed histological correlation in 76.7% of head and neck appendageal tumors.

Limitations

The major limitation of our study was a single biopsy for each patient; multiple biopsies over the disease course might have helped to obtain definite histology in inconclusive cases.

Conclusion

Nodular skin lesions are rare accounting for only 0.45% of all new dermatology outpatients. Benign neoplasms are the commonest cause followed by inflammatory disorders such as prurigo nodularis. However, exclusion of leprosy reactions, especially ENL, is critical in doubtful cases. Although appropriate clinical examination is adequate for diagnosis in most cases, supplementary histopathological

examination is necessary to confirm the same and rule out differentials. So, this study highlights the importance of clinico-pathological correlation for early and definitive diagnosis, to facilitate specific treatment at the earliest.

Author Contribution

All authors contributed equally.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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