Original Article

A Six-Year Retrospective Analysis of Skin Biopsies in the Pediatric and Adolescent Population Performed at a Tertiary Health Care Center in India

Tejas Vishwanath, Vidya Kharkar, Prachi Gole, Sunanda Mahajan, Siddhi Chikhalkar

Department of Dermatology, Seth G.S. Medical College and K.E.M. Hospital, Mumbai, Maharashtra, India

Abstract

Background: Hesitancy to perform skin biopsies in children or adolescents may lead to delayed diagnosis or misdiagnosis and relatively, few studies analyzing pediatric skin biopsies exist. **Aim and Objectives:** This study aims to analyze the spectrum of skin diseases biopsied and demographic data of pediatric patients underwent skin biopsies at a tertiary health care center in India. **Materials and Methods:** Biopsy records over six years were analyzed, noting demographic data, disease duration, clinical differential diagnoses (CDD), final diagnosis after histopathology, disease categorization, and agreement between clinical and final diagnosis. The mean, range, and statistical significance of differences between proportions were calculated. **Results:** A total of 1308 biopsy records were analyzed. A male preponderance was noted (males - 55.1%; *n* = 721, females - 44.9%; *n* = 587). Most biopsies were performed in adolescents (12–18 years; 55.2%) followed by school-age children (5–12 years; 31.4%). Preponderant disease groups biopsied comprised papulosquamous (17.7%; *n* = 231) and infectious diseases (14.1%; *n* = 184). Leprosy was the most common infectious disease (37.5%; *n* = 69) with most patients belonging to borderline tuberculoid spectrum. The overall diagnostic agreement was 74.7%. No correlation of final diagnosis was noted with the number of CDD offered. In more than a fifth of cases, biopsy averted misdiagnosis. **Conclusions:** This study highlights the importance of skin biopsies in pediatric patients and the relatively high clinico-histopathologic agreement. Leprosy and papulosquamous diseases were preponderant in the pediatric dermatopathology caseload.

Keywords: *Dermatology, dermatopathology, pediatric, skin biopsy*

Introduction

Pediatric dermatopathology is an evolving field in the Indian subcontinent.[1,2] This discipline is important since the manifestations and spectrum of skin diseases in children vary from adults, and dermatopathology is often confirmatory.[3,4] Hesitancy to perform skin biopsies in children or adolescents may lead to delayed diagnosis or misdiagnosis. While studies analyzing skin biopsies in adult populations are numerous, fewer such studies in the pediatric age group exist. This study details the spectrum of skin diseases biopsied and clinicopathologic agreement in children in a tertiary center in India.

Materials and Methods

Records of skin biopsy specimens (all performed after written informed consent of the caregiver and assent in case of adolescents) from patients below the age of 18 years from September 2015 to August 2021 were analyzed. Slides were interpreted by at least four consultants, who were dermatopathologists as well as clinicians. Patients whose slides had not been interpreted were excluded.

Patient age, sex, disease duration, history of self-medication, biopsy site and technique, clinical differential diagnosis (CDD) and final diagnosis on histopathology (or clinicopathologic correlation), and admission details were entered into an electronic database (Excel 2013®, Microsoft Corp., Redmond, WA). Age categorization (neonates- <1 month; infants-1 month to <1 year; preschool children-1 year to <5 years; school children-5 years to <12 years; adolescents-12 years to <18 years as per previous study[5]) and disease categorization were performed. Agreement between

How to cite this article: Vishwanath T, Kharkar V, Gole P, Mahajan S, Chikhalkar S. A six-year retrospective analysis of skin biopsies in the pediatric and adolescent population performed at a tertiary health care center in India. Indian Dermatol Online J 2023;14:500-5.

Received: 04-Dec-2022. **Revised:** 22-Jan-2023. **Accepted:** 23-Jan-2023. **Published:** 28-Jun-2023.

Address for correspondence:
Dr. Prachi Gole, Department of Dermatology, Seth G.S. Medical College and K.E.M. Hospital, Mumbai - 400 012, Maharashtra, India.
E-mail: prachigole2@gmail.com

Access this article online

Website: http://journals.lww.com/IDOJ

DOI: 10.4103/idoj.idoj_654_22

Quick Response Code:

clinical and final diagnoses was ascertained by the same clinicians and dermatopathologists, all of whom had assessed the patient initially. Complete diagnostic agreement implied classical histopathology, which indicated any of the CDDs. Diagnostic disagreement indicated a new diagnosis. Cases with partial concordance had only a part of a CDD on histopathology, e.g., a clinical case of borderline tuberculoid leprosy (BTL) with histopathologic foci of downgrading/reaction along with features of BTL.

Statistical analysis

Mean, range, and percentages were calculated for continuous values. Chi-square tests were performed to ascertain the correlation between the number of CDDs and diagnostic agreement.

Results

Pediatric skin biopsies constituted 12.9% (n = 1498/11656) of the total biopsies performed during the study period. Of these, 1308 patients fulfilled the inclusion criteria; 83.9% (n = 1097/1308) patients underwent a single biopsy and the remaining patients underwent multiple biopsies giving 1531 specimens. In 98% (n = 1282/1308) patients, biopsy was performed for diagnostic indications, whereas, in the remaining 2% (n = 26/1308), it was done for excising a neoplasm. Disease duration ranged from 1 day to 17 years. Table 1 and Figures 1 and 2 depict biopsy data, age and sex distribution, and relative proportion of disease groups diagnosed, respectively. Injection local anesthesia was administered in 96.6% (n = 1256/1308) of patients. In the remaining 3.4% (n = 44/1308) patients, topical anesthesia under occlusion was sufficient since these patients underwent shave biopsy. Oral sedation prior to biopsy was required in 4.7% (n = 61/1308) of patients. The mean age was 12 years (ranging from 2 days to 18 years). Males (55.1%; n = 721/1308) outnumbered females (44.9%; n = 587/1308).

The most common groups of diseases were papulosquamous, followed by infections, and genodermatoses and developmental malformations (GDMs). Among papulosquamous diseases, lichen planus (LP) and related disorders were the most common (50.2%; n = 116/231). Lichen planopilaris (LPP) comprised 50% (n = 22/42) of biopsies performed for trichologic indications. Psoriasis was the second most common papulosquamous disease (28.1%; n = 65/231); psoriasis vulgaris was most prevalent (63.1%; n = 41/65), followed by guttate and pustular psoriasis (23.1%; n = 15/65), plantar, nail, and other variants. Pityriasis lichenoides chronica was diagnosed in 12.1% of patients (n = 28/231).

Among infections, leprosy (37.5%; n = 69/184), followed by tuberculosis (29.9%; n = 55), were preponderant. Most leprosy patients (78.3%; n = 54/69) were adolescents.

Table 1: Biopsy site, technique and indication data

Site
Lower limbs- 32.5% (n = 498)
Upper limbs- 24.7% (n = 378)
Trunk- 20.1% (n = 307)
Face- 13.1% (n = 201)
Scalp- 5.8% (n = 89)
Others (including mucosa, genitals, and nails)- 3.8% (n = 58)
Technique of Biopsy
Punch biopsy- 95.5% (n = 1462)
Shave biopsy- 2.9% (n = 44)
Excision (elliptical) biopsy- 1.6% (n = 24)
Wedge biopsy- 0.1% (n = 1)
Indication
Diagnostic- 98.3% (n = 1505)
Therapeutic- 1.7% (n = 26; all neoplastic etiology)

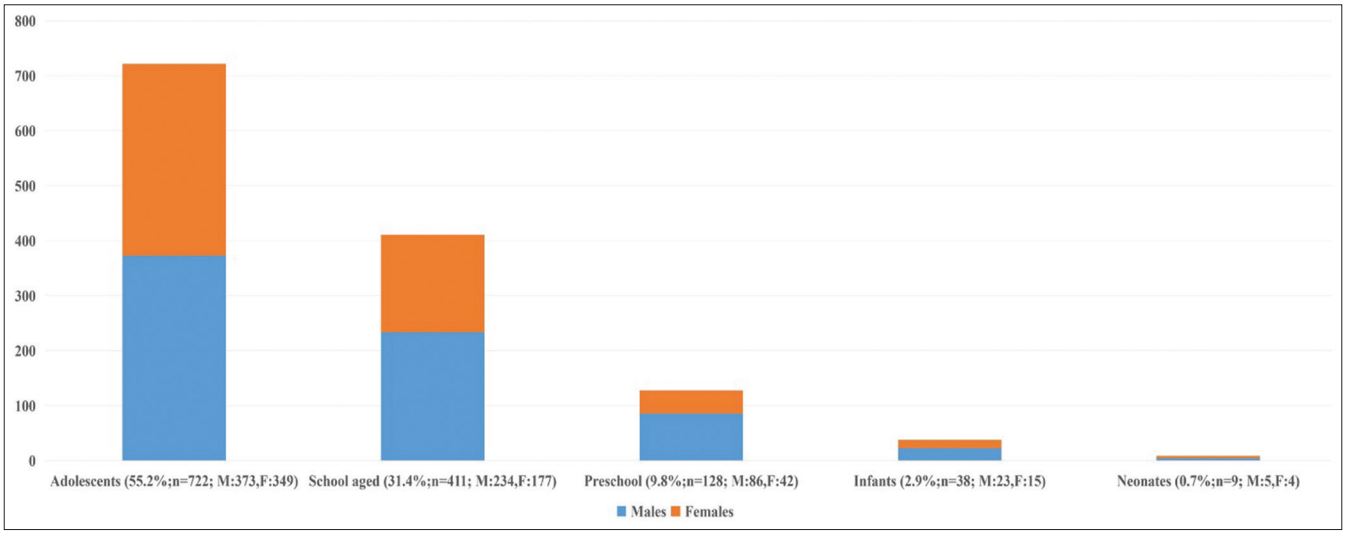

Figure 1: Age distribution of patients biopsied. Adolescents were more commonly biopsied, similar to previous studies. The relatively larger population of adolescents and older children requesting dermatology consultation and their willingness to undergo biopsy contributes to this observation. In all age groups, males outnumbered females

Males (73.9%; *n* = 51/69) outnumbered females (26.1%; *n* = 18/69). Half of the leprosy patients presented within one year of onset of complaints. Borderline tuberculoid leprosy was the most commonly diagnosed (60.9%; *n* = 42/69). Lesions were mostly on exposed areas (limbs-68.1%; *n* = 47/69 and face-23.2%; *n* = 16/69). Diffuse granulomas and foamy changes (signifying downgrading and multibacillary leprosy) were noted in 11.9% (*n* = 5/42) of clinically diagnosed paucibacillary BTL cases. Lepra reactions were diagnosed in 14.5% (*n* = 10/69) of patients. Clinicopathologic mismatch was noted in 23.2% (*n* = 16/69) patients. Among histopathologically proven leprosy patients, 4.3% (*n* = 3/69) were clinically misdiagnosed as vitiligo, contact dermatitis, and systemic lupus erythematosus.

Among the cases of tuberculosis (*n* = 55), lichen scrofulosorum was the most common tuberculid (27.3%; *n* = 15/18). 77.8% (*n* = 14/18) of patients with tuberculids were diagnosed with tuberculosis after histopathology since no other clinical features were noted. Lupus vulgaris was the most common form of tuberculosis (34.5%; *n* = 19/55). One patient with recalcitrant scrofuloderma had an underlying interleukin 12 receptor defect.

Among GDMs (*n* = 127), 74% (n = 94/127) patients presented after one year of disease onset. Two major subgroups in this category were epidermolysis bullosa (27.6%; *n* = 35/127) and hereditary disorders of cornification (21.3%; *n* = 27/127). Most patients presented after one year of disease onset due to lack of awareness and self-medications.

Among patients with inflammatory vascular diseases (*n* = 112) [small vessel vasculitis (*n* = 91) and vasculopathies (*n* = 21)], 89.3% (*n* = 100/112) presented within six months of disease onset. Direct immunofluorescence (DIF) (performed in 24/91 patients of vasculitis) confirmed immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura) in 24.2% (*n* = 22/91) patients.

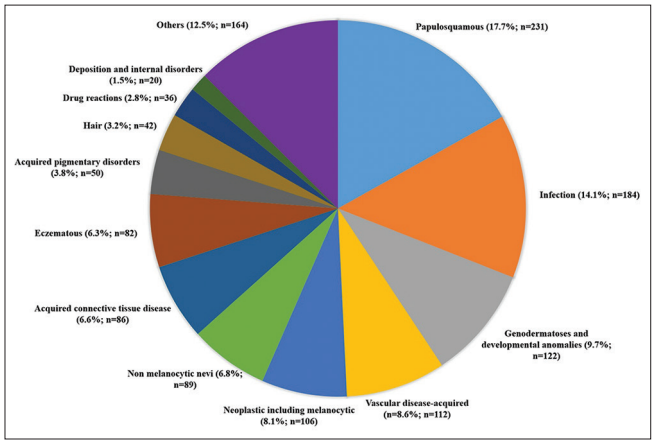

Figure 2: Proportion of various pediatric dermatoses diagnosed with the aid of histopathology. Note the preponderance of papulosquamous diseases and infectious dermatoses, the latter being common in developing and tropical countries such as India

Eczematous/spongiotic dermatitis constituted 6.3% (*n* = 82/1308), of cases of which subacute and chronic eczema (54.4%; *n* = 44/82) were most commonly diagnosed.

Acquired pigmentary disorders comprised 3.8% (50/1308) of patients. Hyperpigmentation disorders were more commonly biopsied (64.7%; *n* = 33/51). Of these, LP pigmentosus/erythema dyschromicum perstans (EDP) constituted the most common subgroup (54.9%; *n* = 28/51). Histopathologic differentiation of these two entities was impossible.

Cutaneous adverse drug reactions (CADRs) constituted 2.8% (*n* = 36/1308) of cases. Most patients (72.2%; *n* = 26) had non-life-threatening CADRs such as morbilliform rash. Stevens-Johnson syndrome and toxic epidermal necrolysis comprised 40% (*n* = 4/10) of severe CADRs. In 58.3% (*n* = 21/36), the culprit drugs were beta-lactams or anti-tuberculous drugs.

Neoplastic lesions (including melanocytic) were biopsied in 8.1% (*n* = 106/1308) patients. Benign neoplasms (cysts, benign appendageal tumors, etc.,) comprised 61.3% (*n* = 65/106) of patients. Melanocytic lesions comprised 26.4% (*n* = 28/106); 67.9% (*n* = 19/28) were diagnosed with melanocytic nevi. Histiocytic neoplasms constituted 12.3% (*n* = 13/106) of patients; 46.2% (*n* = 7/13) had multisystem Langerhans cell histiocytosis. This, along with one case of leukemia cutis, constituted the malignancies diagnosed in this series.

The number of pediatric skin biopsies fell during the COVID-19 pandemic from an average of 22–23 biopsies per month to 3 biopsies from March to December 2020 and 69 biopsies from January to August 2021.

Patients with severe diseases who were admitted constituted 9.8% (*n* = 128/1308) of cases. Vasculopathies and vasculitis were preponderant followed by collagen vascular diseases [Table 2].

Overall, diagnostic agreement was complete in 74.7% (*n* = 977/1308) patients, partial in 1.8% (*n* = 23) patients, and absent in 21% (*n* = 275) patients [Figure 3].

Table 2: Severe skin diseases biopsied in admitted patients

Disease group	Number of patients	Percentage
Vasculitis and vasculopathies	37	29.1
Connective tissue diseases	22	17.3
Genodermatoses	17	13.4
Infection	15	11.8
Severe drug reactions	10	7.9
Papulosquamous (psoriasis)	8	6.3
Neoplastic diseases	8[#]	6.3
Pemphigus vulgaris	5	3.9
Others	5	3.9

[#]Seven patients of multisystem Langerhans cell histiocytosis and one with leukemia cutis

Among patients with a complete clinicopathologic agreement, in 62% (n = 606), one clinical diagnosis was offered. In the remaining patients, the final diagnosis most commonly agreed with the first CDD followed by the second, third, and fourth, and both first and second CDDs [Figure 4]. Diagnostic agreement was maximum in vasculitis/vasculopathies (89.2%) and least in eczematous dermatitis (50%). In 72.8% (n = 952/1308) of patients, histopathology sufficed for the final diagnosis. In the remaining patients, clinicopathologic correlation (CPC) and/or supportive investigations were needed. Repeat biopsy was performed in 0.15% (n = 2/1308) patients due to the inabilility to achieve diagnosis despite clinicopathologic correlation (CPC) (one patient each of ocular LP suspected to be mucous membrane pemphigoid and angioedema clinically suspected to be immunoglobulin G4 disease (IgG4 disease)). Parental concerns and diagnosis (clinched either on histopathology or on CPC) obviated this eventually in the vast majority of cases. The diagnostic agreement did not correlate with the number of CDDs ($P > 0.05$).

Discussion

Dermatologic problems comprise around 30% of pediatric outpatient visits, and may not mirror adult presentations clinically or histopathologically.[3,4,6] Skin biopsy is important in pediatric dermatology since it is often diagnostic.[7] While there are numerous studies on the spectrum of pediatric dermatoses, analysis of pediatric skin biopsies are relatively few. Therefore, analyzing various aspects of this procedure assumes importance.

The present study is among the largest of its kind. It was conducted at a public-sector tertiary healthcare center in India with referrals from adjacent pediatric and oncology centers. These institutions serve large, diverse patient loads from across the Indian subcontinent. Across disease groups (apart from collagen vascular and hair disorders), male preponderance was noted. Geographic factors affecting skin disease and cultural diversity could account for this variation. Table 3 depicts the comparison with previous studies.[6-10]

Preponderance of papulosquamous and infectious dermatoses, especially chronic mycobacterial infections such as leprosy and cutaneous tuberculosis in this study, contrasts with Western and Middle Eastern data where neoplastic conditions were more commonly biopsied.[9,10]

Papulosquamous diseases, although most common, were biopsied less compared to other studies since dermoscopic findings (which are well-defined in many of these diseases) were often diagnostic; caregivers also preferred to avoid biopsy owing to fear of an invasive modality.[6,8] Unlike D'Costa[8] and Ozkanli[9], who found that psoriasis was predominant, LP (and related disorders including LPP) were preponderant in this study. These findings reflect the relatively high incidence of LP in South Asians.[7,11] The relatively high proportion of LPP in this study has not been reported in similar previous studies.

Histopathology in leprosy and tuberculosis is confirmatory and averts misdiagnosis (especially since leprosy can mimic many other diseases). Leprosy, in particular, multibacillary cases remain prevalent in children.[12] Histopathology detects downgrading and reactions in leprosy which may predate clinical features and possibly alter the treatment since clinicopathologic mismatch is a known feature.[13] The considerable prevalence of leprosy in the present study (as in previous Indian studies) is concerning since it points to continuing transmission.[7,8] No patient was <5 years of age, probably due to the long incubation period of the disease even after early acquisition. Lesions on exposed areas contributed to patients' awareness. Similar to previous observations, males were more affected and lepra reactions were less common than in adults.[14,15]

Lichen scrofulosorum was the most common tuberculid, similar to previous observations.[16] Lupus vulgaris, the

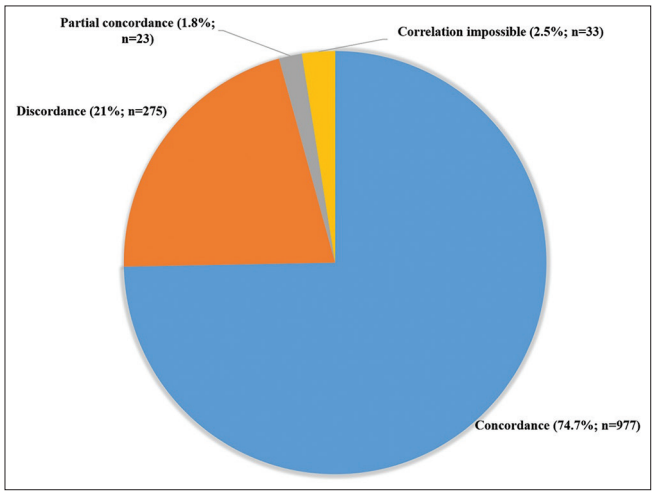

Figure 3: Proportion of agreement, partial agreement, and disagreement between clinical and histopathologic diagnoses and cases where such correlation was not possible. Most of the cases had diagnostic concordance. In 30 (2.4%) patients, histopathology was not contributory owing to artifacts

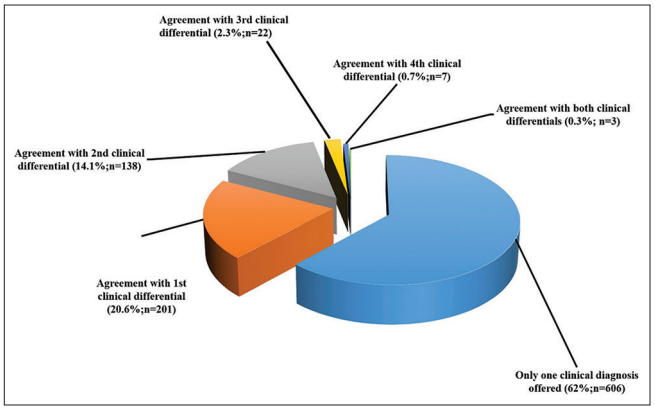

Figure 4: Among cases with clinicopathologic agreement, in most cases, only one clinical diagnosis was offered which was confirmed on biopsy. Among cases with multiple differential diagnoses, in most, the diagnosis was the first or second differential

Table 3: Comparison with similar studies[6-10]

	Present study	Shetageri[6]	Solanki[7]	D'Costa[8]	Ozkanli[9]	Theiler[10]
Duration	6 years (retrospective)	2 years	3 years	2 years (18 months retrospective, 6 months prospective)	3 years	2 years
Sample size	1308	115	85	107 (77 prospective, 30 retrospective)	566	506
Percentage of total biopsies	12.9	12.4	Not mentioned	10.8	10.9	11
Papulosquamous (%)	17.7 (*n*=231)	31.3	15.3	18.7	24	2.6
Infections (%)	14.1 (*n*=184)	7.8	23.5	24.3	3.1	0
Genodermatoses, malformations, and developmental anomalies (%)	9.7 (*n*=127)	15.6	0	6.5	2.1	0
Acquired vascular disease (vasculitis and vasculopathies) (%)	8.6 (*n*=112)	5.2	0	0.9	21.2	0
Neoplastic including melanocyte proliferations (%)	8.1 (*n*=106)	5.2	11.8	4.7	16.8	81
Non-melanocytic nevi (%)	6.8 (*n*=89)	1.7	3.5	1.9	0.3	3
Acquired connective tissue disease (%)	6.6 (*n*=86)	2.6	8.2	3.7	2.4	0
Eczematous diseases (%)	6.3 (*n*=82)	1.7	2.4	6.5	5.4	4
Pigmentary disease (%)	3.8 (*n*=50)	5.2	2.4	7.5	4.2	0
Concordance (%)	74.6 (*n*=977)	82.6	80	56.1	Not mentioned	84
Discordance (%)	21 (*n*=275)	17.4	10	26.2	Not mentioned	16

most common form of tuberculosis in this study, indicates high immunity against *Mycobacterium tuberculosis* due to universal Bacillus Calmette–Guérin (BCG) vaccination at birth in India. Diagnosing cutaneous forms of tuberculosis including tuberculids, which often manifest subtly, is important for appropriate management even in non-endemic countries due to population displacement and migration.

Eczematous dermatoses were biopsied mainly to rule out psoriasis. Adolescents constituted the most common age group, unlike D'Costa and Ozkanli, where younger children were commonly biopsied.[8,9] Diagnosing the cause of spongiotic dermatitis on histologic examination is frequently challenging. In many cases, clinical information and noninvasive investigations such as patch testing were sufficient for diagnosis.[9] Therefore, the true prevalence and etiology cannot be estimated using biopsy data alone.

The proportion of acquired pigmentary disorders was similar to previous studies from India.[6,8] Although, not uncommon in children, biopsies are infrequent since clinical findings and bedside tools such as Wood's lamp and dermoscopy often reveal the diagnosis. Lichen planus pigmentosus and EDP constituted the most common hyperpigmentation disorders and are commoner in darker skin types.[17]

The proportion of neoplastic diseases biopsied was significantly lower than Ozkanli and Theiler.[9,10] The paucity of melanocytic lesions is similar to previous studies in higher Fitzpatrick skin types.[18,19] In no case was a malignancy diagnosed histologically when it was not clinically suspected.

Histopathology gave clinically relevant additional information on vasculitis (disease activity and consequently, need for therapy), leprosy (features of downgrading and reaction), and LPP (disease activity and prognosis). Epidermolytic hyperkeratosis was noted in two patients clinically diagnosed as verrucous epidermal nevus. This finding assumes importance since, if the pathogenic variant involves the germline, epidermolytic ichthyosis may manifest in the offspring.[20]

Factors contributing to the relatively high overall diagnostic accuracy included interpretation by multiple experienced clinicians as well as dermatopathologists, all of whom had assessed patients initially. In case of difficult-to-diagnose slides, departmental discussions and collaboration with referring pediatricians were conducted. Classic histopathologic features and investigations such as DIF contributed to high diagnostic accuracy in vasculitides and vasculopathies. In eczematous dermatoses, however, clinical information and investigations assume importance; also home remedies (noted in biopsy records) were commonly resorted to by these patients altering the clinical picture.

The chief drawback of this study is its retrospective nature. Patient entries with missing histopathologic data were excluded. Future studies could include dermoscopic analysis as well.

Conclusion

Histopathology, although confirmatory in the majority of cases, supplements (and does not substitute for) history taking, examination, and bedside tests, including

dermoscopy. The prevalence of chronic mycobacterial infections in pediatric dermatopathology in our institution highlights the need for awareness and continuing vigilance. In an era of population displacement, leprosy and tuberculosis may be expected to be on the upswing in migrant destinations as well.

Increased awareness among pediatricians about skin conditions needing biopsies, establishment of electronic medical records of photomicrographs, and closer collaboration between referring physicians and pathologists may further increase diagnostic accuracy in the future.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Afsar FS, Diniz G, Aktas S. Pedıatrıc dermatopathology: An overvıew. Arch Argent Pediatr 2017;115:377-81.
2. Essary LR, Hoang MP, Carder KR. Practical review and recent developments in pediatric dermatopathology. Adv Dermatol 2005;21:193-215.
3. Paller A, Mancini A. An overview of dermatologic diagnosis and procedures. In: Paller A, Mancini A, editors. Clinical Pediatric Dermatology. 6th ed. St. Louis: Elsevier; 2016. p.1.
4. Nandakumar G. Skin biopsy in pediatric age group: Special considerations. Indian J Paediatr Dermatol 2012;13:35-7.
5. Sardana K, Mahajan S, Sarkar R, Mendiratta V, Bhushan P, Koranne RV, *et al.* The spectrum of skin disease among Indian children. Pediatr Dermatol 2009;26:6-13.
6. Shetageri SN, Roopa AN, Parthiban R, Rekha TP, Shruthi H. Histopathological spectrum of pediatric skin biopsies in a rural setup. Indian J Pathol Oncol 2019;6:284-92.
7. Solanki A, Chauhan A. Clinicohistopathological profile of 85 pediatric patients attending skin outpatient department: A retrospective analysis at a municipal hospital of middle-east region of Ahmedabad. Indian J Paediatr Dermatol 2016;17:258-62.
8. Grace DF, Bendale KA, Patil YV. Spectrum of pediatric skin biopsies. Indian J Dermatol 2007;52:111-5.
9. Ozkanli S, Zemheri E, Zindanci I, Kuru B, Zenginkinet T, Karadag AS. Three years of retrospective evaluation of skin biopsy results in childhood. North Clin Istanb 2015;2:48-54.
10. Theiler M, Neuhaus K, Kerl K, Weibel L. The spectrum of skin biopsies and excisions in a pediatric skin center. Eur J Pediatr 2017;176:1663-8.
11. Balasubramaniam P, Ogboli M, Moss C. Lichen planus in children: Review of 26 cases. Clin Exp Dermatol 2008;33:457-9.
12. Palit A, Inamadar AC. Childhood leprosy in India over the past two decades. Lepr Rev 2014;85:93-9.
13. Chadha AA, Dongre A, Khopkar US. A single centre cross-sectional study of clinicopathological correlation in leprosy: Discordance and spectral shift. Indian J Lepr 2021;93:143-56.
14. Narang T, Kumar B. Leprosy in children. Indian J Paediatr Dermatol 2019;20:12-24.
15. Jindal N, Shanker V, Tegta GR, Gupta M, Verma GK. Clinicoepidemiological trends of leprosy in Himachal Pradesh: A five year study. Indian J Lepr 2009;81:1739.
16. Kumar B, Kumar S. Pediatric cutaneous tuberculosis: Indian scenario. Indian J Paediatr Dermatol 2018;19:202-11.
17. Mathews I, Thappa DM, Singh N, Gochhait D. Lichen planus pigmentosus: A short review. Pigment Int 2016;3:5-10.
18. Gallagher RP, Rivers JK, Yang CP, McLean DI, Coldman AJ, Silver HK. Melanocytic nevus density in Asian, Indo-Pakistani, and white children: The vancouver mole study. J Am Acad Dermatol 1991;25:507-12.
19. Senthilkumar M, Thappa DM. Melanocytic nevi in children: A clinical study. Indian J Dermatol 2006;51:26-9.
20. Ang P, Tay YK. Linear epidermolytic epidermal naevus--A case report. Singapore Med J 1998;39:220-1.