Original Investigation
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Retrospective evaluation of 28 cases of inflammatory linear verrucous epidermal nevus

Enflamatuvar lineer verrüköz epidermal nevüs: 28 olgunun retrospektif değerlendirmesi

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Abstract

Background and Design: Inflammatory linear verrucous epidermal nevus (ILVEN) is a rare, chronic dermatosis characterized by linear erythematous scaly plaques following Blaschko's lines. This study aims to comprehensively evaluate ILVEN cases, focusing on demographic, clinical, and histopathological features to improve understanding of its presentation and management.
Materials and Methods: This retrospective cross-sectional study included 28 patients diagnosed at our center with clinically and histopathologically confirmed ILVEN between 2011 and 2022. Data on patient demographics, age at lesion onset, duration before diagnosis, lesion location, histopathological findings, and treatment approaches were collected from hospital records and supplemented by patient interviews.
Results: Our study had a male predominance (63.4%), with a median age of lesion onset at 7.5 years and a median age of 14 years, indicating a prolonged delay in diagnosis. The mean duration from lesion onset to diagnosis was 9.86 years. Lesions were most frequently located on the lower extremities, following a Blaschkoid distribution, with 73.3% of patients reporting pruritus. Key histopathological findings included orthokeratosis with hypergranulosis (60.7%), parakeratosis overlying hypogranulosis (46.4%), and psoriasiform epidermal hyperplasia (46.4%). Topical corticosteroids were the primary treatment modality, while spontaneous regression was observed in 14.3% of untreated cases.
Conclusion: This study highlights the clinical and histopathological features of ILVEN, emphasizing the importance of early recognition in reducing diagnostic delays. Further research is warranted to enhance understanding of ILVEN's clinical course and to optimize diagnostic and therapeutic strategies.
Keywords: ILVEN, Epidermal nevus, Linear dermatosis

Öz

Amaç: Enflamatuvar lineer verrüköz epidermal nevüs (ILVEN), Blaschko çizgilerini izleyen lineer eritematöz, skuamlı plaklarla karakterize nadir ve kronik bir dermatozdur. Bu çalışma, ILVEN'in sunumu ve yönetimi hakkında daha fazla bilgi sağlamak amacıyla olguları demografik, klinik ve histopatolojik özellikler açısından kapsamlı bir şekilde değerlendirmeyi amaçlamaktadır.
Gereç ve Yöntem: Bu retrospektif kesitsel çalışmaya, 2011-2022 yılları arasında merkezimizde klinik ve histopatolojik olarak ILVEN tanısı doğrulanmış 28 hasta dahil edilmiştir. Hastaların demografik verileri, lezyon başlangıç yaşı, tanıya kadar geçen süre, lezyon yerleşimi, histopatolojik bulgular ve tedavi yaklaşımlarına ilişkin veriler hastane kayıtlarından toplanmış ve hasta görüşmeleri ile desteklenmiştir.
Bulgular: Çalışmamızda erkek hastalar çoğunluktaydı (%63,4) ve lezyon başlangıç yaşı ortancası 7,5 yıl, tanı yaşı ortancası 14 yıl olarak bulunmuş olup, tanıda belirgin bir gecikme olduğunu göstermektedir. Lezyon başlangıcından tanıya kadar geçen ortalama süre 9,86 yıl olarak saptanmıştır. Lezyonlar en sık alt ekstremitelerde, Blaschkoid dağılımda bulunmuş ve hastaların %73,3'ü kaşıntı bildirmiştir. Ana histopatolojik

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bulgular hipergranülozis ile ortokeratoz (%60,7), hipogranülozis üzerinde parakeratoz (%46,4) ve psoriasiform epidermal hiperplazi (%46,4) şeklindedir. Ana tedavi yöntemi topikal kortikosteroidler olup, tedavi almayan hastaların %14,3'ünde spontan gerileme gözlenmiştir.
Sonuç: Bu çalışma, ILVEN'in klinik ve histopatolojik özelliklerini vurgulayarak erken tanının tanı gecikmelerini azaltmadaki önemine dikkat çekmektedir. ILVEN'in klinik seyrini daha iyi anlamak ve tanı ile tedavi stratejilerini optimize etmek için daha fazla araştırmaya ihtiyaç vardır.
Anahtar Kelimeler: İLVEN, Epidermal nevüs, Lineer dermatozlar

Introduction

Inflammatory linear verrucous epidermal nevus (ILVEN), first described by Altman and Mehregan[1], is a rare skin disorder characterized by a linear pattern of erythematous scaly papules and plaques of various sizes following Blaschko's lines. Although it is usually congenital or seen in early childhood, it can rarely be seen in adulthood[1-3]. It is thought to be more common in women than men, and most commonly involves the lower extremities[1,2]. Central nervous system and skeletal anomalies may also be observed. Rarely, oral and mucosal lesions have been reported[4]. The classic histology of ILVEN is psoriasiform acanthosis with overlying alternating parakeratosis and orthokeratosis and corresponding hypo- and hypergranulosis underneath[5]. The differential diagnosis should consider disorders with similar distribution patterns, such as non-inflammatory epidermal nevus, linear psoriasis, linear lichen planus, and lichen striatus[6]. Although multiple case reports on ILVEN are available, there remains a notable lack of larger descriptive studies that can provide a broader understanding of its demographic, clinical, and histopathologic characteristics of ILVEN.

In this study, we aimed to comprehensively assess patients' demographic, clinical, and histopathologic characteristics with a confirmed clinical and histopathologic diagnosis of ILVEN. Additionally, we sought to explore whether specific demographic or clinical features in our cohort align with or differ from those reported in existing literature, with particular attention to possible gender-related differences.

Material and Methods

Study Design

This study was a retrospective, cross-sectional analysis conducted at our dermatology department. It included patients diagnosed with ILVEN between 2011 and 2022.

Setting and Participants

Eligible participants were identified through a rigorous review of medical records within the hospital's information system. Inclusion criteria required both clinical and histopathological confirmation of ILVEN. Out of 66 patients who had undergone biopsy with a preliminary diagnosis of ILVEN, 28 met the inclusion criteria based on verified clinical and histopathological findings. Patients without conclusive diagnostic confirmation were excluded to ensure diagnostic precision. Missing or incomplete data were meticulously supplemented through follow-up telephone interviews with patients or, where applicable, their legal guardians to complete the dataset. Informed consent for photography was obtained from parents or legal guardians for minor patients, following ethical guidelines. Ethics committee approval was obtained for the study (approval number: 406, date: 23.12.2022).

Variables and Data Sources

For each patient, demographic data (gender, age at presentation, and age of lesion onset) and clinical characteristics (lesion duration, location, distribution pattern, and presence or absence of pruritus) were documented based on hospital records. Histopathological findings were recorded from biopsy reports, with all variables carefully corroborated by available clinical records and, where necessary, follow-up interview responses to ensure data completeness. Treatment modalities were classified by the primary intervention type, with spontaneous regression, if observed, also noted. The selected variables were based on established ILVEN characteristics in the literature to support a comprehensive analysis.

Bias

Potential sources of bias were meticulously addressed by rigorously validating hospital record data with interview-obtained information, particularly for variables where data completeness was crucial. Given the retrospective nature of data collection, there was a potential for recall bias, especially concerning lesion duration and age of onset; however, structured interview protocols and verification against hospital records were used to enhance reliability and accuracy in reported information, ensuring the highest level of objectivity in our study.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 24.0 (SPSS Inc., Chicago, IL, USA). Given the data's non-parametric distribution, continuous variables were summarized using descriptive statistics and presented as median values with minimum and maximum ranges. The normality of continuous variables was assessed via histograms and Q-Q plots. Continuous variables were compared between subgroups using the Mann-Whitney U test, and categorical variables were analyzed using Pearson's chi-square test. A significance threshold of $p<0.05$ was applied to all statistical tests.

Results

Participant Flow

The study initially identified 66 patients with a preliminary diagnosis of ILVEN; however, only 28 patients met the inclusion criteria after clinical and histopathological confirmation. All patients were included due to missing data, as any incomplete information was supplemented through follow-up interviews with the patients or their legal guardians.

Descriptive Data

The final cohort included 18 males (63.4%) and 10 females (36.6%), with a median age of 10 years at the time of presentation (Table 1). The mean age at lesion onset was 10.07±15.22 years, with a median of 7.5 years and a range from 0 to 77 years. No statistically significant difference in age of onset was observed between genders ($p=0.470$). The median duration of lesions before clinical presentation was 4.0 years (mean =9.86±12.32 years, range =0.2 to 48.0 years), with no significant gender differences ($p=0.104$). The mean age at diagnosis was 19.93±16.93 years, with a median of 14 years and a range of 2 to 78 years, also showing no significant gender-based differences ($p=0.259$).

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Clinical Characteristics and Outcome Data

Lesion location varied, with the most common sites being the lower extremities (12 patients, 42.9%), followed by the upper extremities (9 patients, 32.1%), head and neck (4 patients, 14.3%), and trunk (3 patients, 10.7%). Anogenital involvement was identified in one patient (3.6%) (Figure 1). Pruritus was reported by 73.3% of the patients, while 26.7% were asymptomatic. No associated congenital anomalies were detected in any of the patients. Most lesions (89%) followed a Blaschkoid distribution, 82% exhibited a verrucous texture, and 75% displayed scaling. Regarding lesion morphology, plaques were the predominant presentation (93%), while papules were observed in 7%. Representative clinical photographs are presented in Figures 2 and 3.

Differential diagnoses considered included non-inflammatory epidermal nevus (20 patients, 71.4%), linear psoriasis (15 patients, 53.6%), linear lichen planus (11 patients, 39.3%), lichen striatus (9 patients, 32.1%), and verruca plana (7 patients, 25%).

Histopathological examination revealed orthokeratosis with hypergranulosis in 60.7% of patients (17 patients), parakeratosis overlying hypogranulosis in 46.4% (13 patients), psoriasiform epidermal hyperplasia in 46.4% (13 patients), papillomatosis in 39.3% (11 patients), and acanthosis in 32.1% (9 patients) (Table 1, Figure 4).

Topical corticosteroids were the primary treatment modality for 39.3% of patients, followed by a combination of topical corticosteroids and emollients (17.9%). Cryotherapy and laser therapy were each applied in 3.6% of cases. Spontaneous regression occurred in 14.3% of untreated patients, observed during follow-up (Table 1).

Discussion

Key Results

This study provides a detailed evaluation of the demographic, clinical, and histopathological characteristics of patients with confirmed ILVEN. Our study indicates a male predominance, with 63.4% of patients being male. This finding contrasts with earlier studies that reported a higher prevalence of ILVEN in females. For example, Altman and Mehregan[1], reported a 4:1 female-to-male ratio in their cohort of 25 patients, suggesting that females were more commonly affected. However, our findings are consistent with those of Lee and Rogers[2] who found that 70% of their 23 patients were male. The variability in gender distribution across studies may be attributed to differences in sample size, population demographics, or even regional variations in the disease's presentation. It is important to note that the reasons for this observed gender difference remain unclear. While earlier studies suggested hormonal or genetic factors might play a role, no definitive explanations have been established. Further large-scale studies are

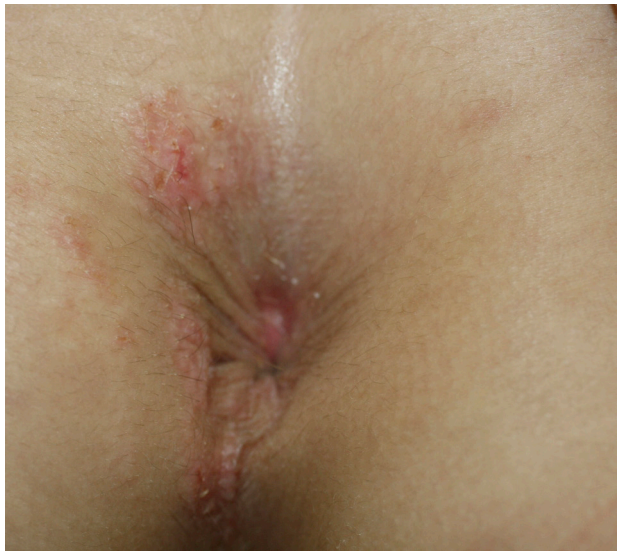

Figure 1. Scattered plaque in the anogenital area is verrucous in places and compatible with ILVEN, in which scale is seen

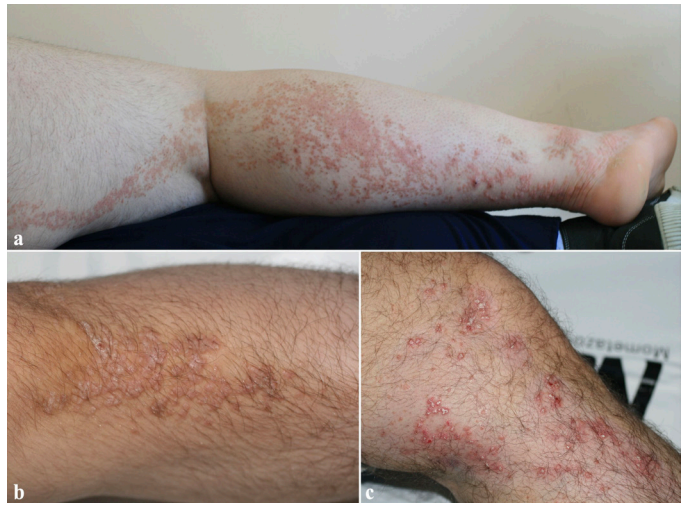

Figure 2. (a) Plaque with blaschkoid distribution, erythematous, verrucous appearance extending from the posterior right thigh to the ankle. **(b)** Plaque in the right peripatellar area, consisting of many papules with a linear distribution, verrucous appearance, and pinkish color, tends to merge. **(c)** Erythematous scaly plaque with blaschkoid distribution and verrucous appearance extending from the left peripatellar region to the center of the cruris

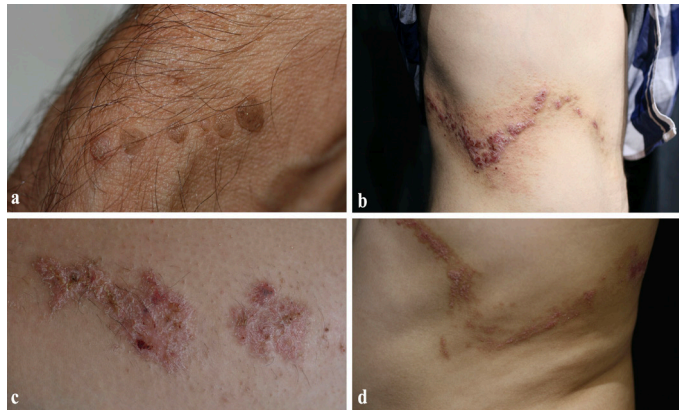

Figure 3. (a) Plaque consisting of linearly distributed, verrucous, brownish papules in the flexor region of the right forearm. **(b)** Erythematous scaly plaque with blaschkoid distribution, verrucous appearance on the left side of the trunk. **(c)** Linearly distributed, verrucous, erythematous plaque with a mild scaly appearance on the posterior thigh. **(d)** A mildly erythematous brownish plaque with blaschkoid distribution and a verrucous appearance is located on the left side of the trunk

needed to explore whether these gender differences are consistent across diverse populations and what factors may contribute to ILVEN's variable presentation between males and females.

The broad age range at diagnosis and prolonged delay in clinical presentation observed in our study align with the indolent progression of ILVEN reported in prior studies. Altman and Mehregan[1], found that while ILVEN often presents before age five, the mean duration of lesions before diagnosis was approximately six years, highlighting this condition's persistence and often overlooked nature.

Our study observed a slightly higher mean age of onset and an extended diagnostic timeline, including one unique case presenting at 77. Although ILVEN generally manifests in childhood, cases with late-onset presentation have also been reported in the literature, suggesting that ILVEN may occasionally emerge in later decades of life[3,7,8].

Table 1. Characteristics of ILVEN Patients (n=28)

Characteristic	Frequency (n, %)		Mean ± SD	Median (Range)
Demographic Information				
Gender	Male	63.4% (18)		
	Female	36.6% (10)		
Clinical Information				
Age at lesion onset (years)			10.07±15.22	7.5 (0-77)
Duration of lesions (years)			9.86±12.32	4.0 (0.2-48.0)
Age at diagnosis (years)			19.93±16.93	14 (2.0-78.0)
Location of Lesions	Lower extremity	42.9% (12)		
	Upper extremity	31.1% (9)		
	Head and neck	14.3% (4)		
	Trunk	10.7% (3)		
	Anogenital region	3.6% (1)		
Symptoms	Itching	73.3% (20)		
	Asymptomatic	26.7% (8)		
Distribution of Lesions	Blaschkoid	89% (25)		
	Verrucous appearance	82% (23)		
	Scaling	75% (21)		
Appearance of Lesions	Plaque	90% (26)		
	Papule	10% (2)		
Histopathological Findings	Orthokeratosis with hypergranulosis	60.7% (17)		
	Parakeratosis over hypogranulosis	46.4% (13)		
	Psoriasiform epidermal hyperplasia	46.4% (13)		
	Papillomatosis	39.3% (11)		
	Acanthosis	32.1% (9)		
Differential Diagnosis	Non-inflammatory epidermal nevus	71.4% (20)		
	Linear psoriasis	53.6% (15)		
	Linear lichen planus	39.3% (11)		
	Lichen striatus	32.1% (9)		
	Verruca plana	25% (7)		
Treatment Methods	Topical corticosteroids	39.3% (11)		
	Topical corticosteroids and emollient	17.9% (5)		
	Cryotherapy	3.6% (1)		
	Laser Therapy	3.6% (1)		
	Spontaneous regression	14.3% (4)		
Other Findings	Associated anomalies	None		
	Family history	None		

ILVEN: Inflammatory linear verrucous epidermal nevus, SD: Standard deviation.

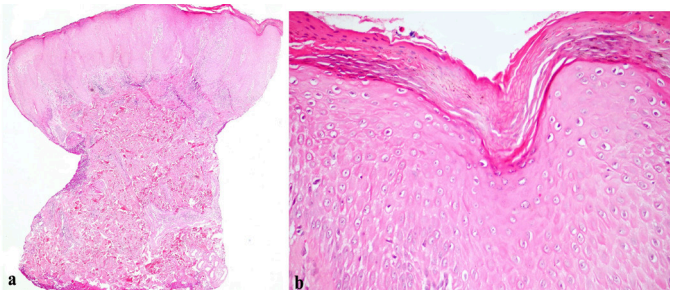

Figure 4. (a) Psoriasiform epidermal hyperplasia (HE x 100) **(b)** Alternating orthohyperkeratosis and parakeratosis areas are observed. The granular layer is reduced/absent in the parakeratosis area. The granular layer can be seen in ortho-hyperkeratosis areas (HE x 400)
HE: Hematoxylin and Eosin staining

These findings underscore the need for prospective studies to elucidate ILVEN's natural history across populations and emphasize the importance of increased clinical awareness to promote earlier diagnosis.

Limitations

This study has several limitations that should be considered when interpreting the results. The study's retrospective nature may introduce recall and selection biases, particularly concerning the age of onset and lesion duration, as some data were supplemented through telephone interviews with patients or their guardians. The relatively small sample size may limit the generalizability of the findings and reduce the statistical power to detect potential differences in demographics or clinical features. As this is a single-center study, findings may reflect local or regional patterns that need to be more generalizable to broader populations. Future studies with more significant, multicenter cohorts must confirm our observations and establish more generalizable findings about ILVEN's demographic and clinical characteristics.

Interpretation

The clinical presentation of ILVEN in our cohort was consistent with previously documented findings. Most lesions followed a Blaschkoid distribution and exhibited verrucous texture and scaling. Plaque morphology was the predominant form, with papules observed less frequently. This aligns with prior studies identifying plaques as characteristic of ILVEN and often forming linear patterns along Blaschko's lines[9,10].

Additionally, 73.3% of our patients reported itching associated with their ILVEN lesions, consistent with the literature, where pruritus is frequently noted as a prominent symptom. Altman and Mehregan[1], initially described ILVEN as often accompanied by pruritus, which can be persistent and resistant to treatment, though some patients may remain asymptomatic[1].

These findings emphasize the typical clinical presentation of ILVEN and the variability in symptom severity, underscoring the importance of individualized management strategies, especially for pruritic cases where standard treatments may offer only temporary relief.

Differentiating ILVEN from other linear dermatoses is essential due to overlapping clinical presentations but distinct histopathological and etiological features.

The histopathological findings in our cohort are consistent with the established patterns in ILVEN, as reported in the literature. Psoriasiform epidermal hyperplasia and alternating orthokeratosis with hypergranulosis and parakeratosis overlying hypogranulosis were among the most common features observed, aligning with descriptions by Altman and Mehregan[1], in their foundational study on ILVEN of orthokeratosis with a thickened granular layer and parakeratosis with a diminished granular layer is characteristic of ILVEN. It is often essential for distinguishing it from other linear dermatoses[1]. Recent studies have further refined the diagnostic approach with immunohistochemical markers, showing lower basal layer Ki-67 positivity and increased keratin-10 expression in ILVEN compared to psoriasis, along with decreased and localized involucrin staining in parakeratotic regions[3]. Additionally, recent studies suggest a genetic basis involving CARD14 mutations in some cases, highlighting the potential role of mosaicism in ILVEN's variable presentation[5]. Given these findings, further genetic studies are warranted to understand ILVEN's pathogenesis better and refine diagnostic and therapeutic approaches.

Our study's most common differential diagnosis was non-inflammatory epidermal nevus, which, although similar in its verrucous appearance, is typically associated with congenital anomalies and lacks the lower extremity predominance seen in ILVEN[11]. The absence of accompanying anomalies in our cases further corroborated the diagnosis of ILVEN, distinguishing it from non-inflammatory epidermal nevus and similar entities.

Linear psoriasis, another frequently considered differential diagnosis, is often adult-onset and shares morphological similarities with ILVEN. However, it exhibits distinct immunohistochemical features, with studies like those by Vissers et al.[12] showing lower Ki-67 positivity, higher keratin-10 positivity, and Human Leukocyte Antigen-DR isotype expression in ILVEN.. In our study, many patients required differentiation from linear psoriasis, and the characteristic alternating ortho- and parakeratosis observed in ILVEN were vital in confirming the diagnosis.

Although linear lichen planus may present in a linear pattern similar to ILVEN, it is characterized by violaceous papules and plaques, later onset, and more intense pruritus. Histopathologically, it also exhibits a band-like lymphocytic infiltrate, differentiating it from ILVEN[13]. In our cohort, ILVEN's earlier onset and Blaschkoid distribution helped to distinguish it from linear lichen planus.

Lichen striatus, which often affects children, is characterized by its spontaneous regression and unique histopathological features, such as lymphocytic infiltrates around sweat ducts[14]. Although a minority of ILVEN cases in our cohort demonstrated spontaneous regression, the persistent Blaschkoid distribution and absence of lichen striatus-specific histopathology were decisive factors favoring ILVEN.

Verruca plana, associated with human papillomavirus (HPV) infection, presents as flat, verrucous, hyperkeratotic lesions and can be differentiated from ILVEN by the histological presence of koilocytes, detection of HPV DNA via PCR, and dermoscopic differences[15].

A range of treatments has been employed in ILVEN cases with varying degrees of success, including topical and intralesional corticosteroids, retinoids, dithranol, 5-fluorouracil, vitamin D analogs, calcineurin inhibitors, surgical excision, cryotherapy, and laser therapies[16,17]. Recently, biological agents have also shown promising results[18].

In our study, topical corticosteroids were the primary treatment modality (39.3%), followed by combinations of corticosteroids and emollients (17.9%), with cryotherapy and laser therapy used less frequently. These interventions align with standard management strategies but typically provide only temporary relief, as ILVEN generally exhibits limited responsiveness to treatment. Notably, spontaneous resolution occurred in 14.3% of untreated patients-a phenomenon occasionally reported in the literature that warrants further investigation to identify potential predictors. Given these findings, further genetic and immunohistochemical research is recommended to optimize treatment protocols and elucidate the factors driving ILVEN's variable clinical course.

Generalisability

Our findings offer valuable insights into ILVEN's clinical and histopathological characteristics; however, the single-center design and the regional focus of the sample may limit their applicability to other populations. Future studies involving broader, more diverse populations across various geographic areas are necessary to enhance the external validity of these results and provide a more comprehensive understanding of ILVEN's demographic variability.

Conclusion

In this study, we evaluated the demographic, clinical, and histopathological characteristics of patients diagnosed with ILVEN, a rare variant of epidermal nevus. Recognizing the clinical and histopathological features of ILVEN is crucial for differentiating it from other linearly distributed dermatological conditions. Although ILVEN typically appears early, patients often delay seeking dermatological care, underscoring the importance of early detection and intervention. Further research is warranted to enhance understanding of ILVEN's clinical course and to optimize diagnostic and therapeutic strategies.

Ethics

Ethics Committee Approval: This study was approved by the ethics board of the University of Health Sciences Türkiye. İstanbul Training and Research Hospital (approval number: 406, date: 23.12.2022).

Informed Consent: Informed consent for photography was obtained from parents or legal guardians for minor patients, following ethical guidelines.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B.D., V.M., C.L., A.E.K.A., Concept: B.B.D., V.M., Design: B.B.D., V.M., Data Collection or Processing: B.B.D., V.M., Analysis or Interpretation: B.B.D., A.E.K.A., Literature Search: B.B.D., Writing: B.B.D., A.E.K.A.

Conflict of Interest: The authors declared that they have no conflict of interest.

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