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Evaluation of Demographic, Clinical, and Histological Characteristics of Spitz Nevus Among Iranian Patients: A Retrospective Study From 2016 to 2021

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ABSTRACT

Background and Aims: Spitz nevus is a rare benign tumor classified among unusual melanocytic nevi. This study aimed to identify the demographic, clinical, and histopathological characteristics of Spitz nevus among Iranian patients.

Methods: This descriptive, retrospective study involved reviewing the records of patients diagnosed with Spitz nevus at a referral and academic hospital in Iran between 2016 and 2021. Data were extracted regarding demographic characteristics, including age, gender, location, clinical symptoms, disease duration, medical history, and medication history. Additionally, biopsied lesions were evaluated for histopathological features.

Results: A total of 86 patients were evaluated, comprising 37 males (43.5%) and 49 females (55.5%). The mean age was 15.6 years (SD ± 14.8). The most common sites of involvement were the upper extremities (23.3%) and face (17.4%). Disease durations of 1 and 2 years were the most prevalent, observed in 24 (27.9%) and 26 patients (30.2%), respectively. Notably, none of the patients had any underlying diseases. Histopathological evaluation revealed compound Spitz nevus in 25 patients (29.4%), junctional Spitz nevus in 14 patients (16.5%), and dermal Spitz nevus in 10 patients (11.8%).

Conclusion: This study provides a comprehensive overview of the demographics, clinical presentation, and histopathological features of Spitz nevus among Iranian patients, highlighting the necessity for ongoing research and innovation in diagnostic techniques.

1 | Introduction

Spitz nevus, also known as spitz melanoma, is a distinctive type of skin lesion that has long perplexed dermatologists and clinicians due to its propensity for mimicry of malignant melanoma [1]. This intriguing neoplasm, characterized by the presence of spindle and/or epithelioid cells, belongs to the category of rare and unusual melanocytic lesions. Over the years, it has garnered attention for its enigmatic behavior, rapid growth during the initial stages, and subsequent stabilization or even spontaneous disappearance [1–3]. Typically, these lesions manifest as papules or unique, symmetric masses with well-defined, elevated borders, displaying a range of colors from skin-toned to shades of red or brown [4].

Histopathologically, spitzoid lesions represent a broad spectrum of melanocytic neoplasias, including benign Spitz nevi, atypical Spitz tumors (ASTs), and malignant spitzoid melanomas, which are very challenging to diagnose. Due to the overlap of histopathological features, ASTs are identified by exclusion. The typical features of Spitz nevi are small, symmetric, well-circumscribed lesions showing uniform cellularity with minimal atypia, while mitoses, if present, are confined to the superficial dermis. In contrast, the ASTs have several intermediary features such as asymmetry, mild to moderate cytologic atypia, increased cellularity, and deeper mitotic figures without the broad invasion features that characterize melanomas. On the contrary, spitzoid melanomas exhibit marked asymmetry, prominent atypia, high mitotic activity, and an invasive growth pattern and are hence put at a much greater risk of metastasis. It is these distinguishing features that render them so crucial in differential diagnosis for categorizing each lesion into one category or another and subsequently guiding proper clinical care.

One such important immunohistochemistry marker is PRAME, or Preferentially Expressed Antigen in Melanoma, which is important in raising diagnostic precision in the differential diagnosis of spitzoid lesions. Hence, Umano et al. [5] commented that in benign Spitz nevi, PRAME expression is usually absent or weak, whereas it shows strong diffuse nuclear staining in spitzoid melanomas, which are those with a higher risk of malignancy. PRAME shows variable expression in ASTs, which reflects their borderline nature. This incorporation of PRAME into the diagnostic work stream provides an objective measure of malignancy risk, helping the differentiation of benign and atypical lesions from those that would require aggressive treatment. The presence or expression of this marker provides information on prognosis, mainly in pediatric patients where it would be impossible to get a satisfactory prognostication from morphologic examination alone, hence helping the clinicians arrive at informed decisions about patient care [5].

Despite specific diagnostic criteria developed for both Spitz nevus and melanoma, the histopathological and histological similarities often blur the lines between these two entities. Furthermore, the elusive etiology of Spitz nevus and its true biological behavior remain subjects of ongoing investigation, hampering our ability to definitively determine appropriate treatment strategies [6, 7]. Hence, there is a pressing need for comprehensive studies that shed light on the demographics, clinical presentation, and pathology of patients with Spitz nevus, offering valuable insights into its diagnosis and management [8, 9]. To the best of our knowledge, this study was the first one in this regard among Iranian patients.

In this study, we embarked on a journey to unravel the intricate tapestry of Spitz nevus by meticulously examining biopsied patients at an academic hospital over 5 years, from 2016 to 2021. We aimed to explore the demographic aspects of Spitz nevus, including age and gender distribution, lesion location, symptomatic presentation, duration of illness, as well as medical and drug history. Furthermore, we tried to delve into the histopathological characteristics of this intriguing neoplasm, leveraging a thorough review of the pathology section to provide a comprehensive understanding of its pathological features, as well as enhance the accuracy of Spitz nevus diagnosis and facilitate its differentiation from other skin conditions, particularly malignant melanoma. This, in turn, will enable healthcare professionals to select appropriate treatment methods, reduce the duration of illness, and minimize potential complications, ultimately improving the overall quality of care for patients with Spitz nevus.

2 | Materials and Methods

This was a retrospective descriptive study conducted on biopsied patients with a confirmed diagnosis of Spitz nevus at an academic hospital over 5 years, from 2016 to 2021. The general aim of this study will be based on demographic, clinical, and pathological features of Spitz nevus in patients who underwent biopsy at Razi Hospital. Secondary objectives will include the prevalence of the patients according to gender, age, location of lesions, histopathological features, duration of illness, history of predisposing conditions, medication use history, and histological nature of the lesions. This study will be advantageous in conducting a more appropriate diagnosis with better differentiation of the Spitz nevus from other diseases, especially melanoma. This will eventually permit the selection of treatment strategies that are appropriate, thereby shortening the duration of the disease and minimizing its complications. In this study, the list of patients, specific to each variable analyzed, will be included in a table. Accordingly, this table has been divided into two parts, the first dealing with demographic information of age and gender, and the second related to the characteristics of the Spitz lesions. The data from patients will be obtained by reviewing patient files and the relevant biopsy slides stored in the archives at Razi Hospital.

The hypotheses for this research were set up as two competing hypotheses, and for convenience, the following hypotheses were thus stated: Hypothesis 0: There is no significant difference in the prevalence of patients by gender, age, location of lesions, histopathological features, duration of illness, history of predisposing conditions, medication use history, and histological characteristics of the lesions. Hypothesis 1: There is a significant difference in the prevalence of patients by gender, age, location of lesions, histopathological features, duration of illness, history of predisposing conditions, medication use history, and histological characteristics of the lesions. This would again outline the relationship of these variables and thereby provide certain insights into the characteristics and distribution of cases with Spitz nevus, thereby helping in the comprehensiveness of understanding the condition. Quantitative data analysis will be performed using SPSS software, version 25, where quantitative variables are presented as means and standard deviations, while qualitative variables will be presented as frequencies and percentages. Moreover, the relationships among variables will be analyzed through Pearson's correlation coefficients, independent *t*-tests, and ANOVA. Ethical considerations will ensure that all information about the patients will be confidential and no interventions will be conducted without consent from the patients themselves.

3 | Result

In this study, 86 patients with Spitz nevus were examined, and the data were assessed and statistically compared based on the study objectives.

Thirty-seven patients (43.5%) were male and 49 patients (55.5%) were female. The mean and standard deviation of patients' age were 15.6 ± 14.8 years. The most common sites of involvement were the upper limbs and face, observed in 20 patients (23.3%) and 15 patients (17.4%), respectively (Figure 1).

More than half of the patients experienced a disease duration of less than 2 years (24 patients (27.9%), 1 year and 26 patients (30.2%), 2 years).

None of the patients had an underlying disease.

As observed in Figure 2, the most common types of histopathology were compound Spitz nevus in 25 patients (29.4%), followed by junctional Spitz nevus in 14 patients (16.5%), and dermal Spitz nevus in 10 patients (11.8%).

As observed in Table 1, the distribution of various histopathological subtypes of lesions among patients highlights the prevalence of different types of Spitz nevi and related conditions. The most common subtype is the compound Spitz nevus, accounting for 29.4% of the cases, followed by junctional Spitz nevus at 16.5%. Dermal Spitz nevi represents 11.8% of the lesions, while Malignant melanoma comprises 9.4%, underscoring the importance of differentiating between benign and malignant entities. Less common subtypes include Intradermal Spitz nevus (5.9%), Dysplastic Spitz nevus (4.7%), and Desmoplastic Spitz nevus (2.4%). Atypical cases and those without atypia are observed in 5.9% each, reflecting the diagnostic challenges that these lesions pose. The category labeled "Variable" accounts for 7.1%, indicating cases with diverse or mixed histopathological features, and a small fraction (1.2%) remained inconclusive, highlighting the occasional complexities in definitive diagnosis. This distribution underscores the need for careful histopathological and clinical evaluation to guide accurate diagnosis and management.

4 | Discussion

This retrospective study investigated the demographics, clinical features, and pathology of patients diagnosed with Spitz nevus. The findings, which include a slight female predominance (55.5%) and a mean age of 15.6 years, are somewhat consistent with the literature, albeit with variations that may reflect geographical or ethnic differences. Spitz nevi, ASTs, and spitzoid melanoma each exhibit distinct clinical, dermoscopic, and histopathological characteristics that are crucial for accurate differential diagnosis. Combining clinico-epidemiological information with histopathological findings plays a central role in guiding clinicians, as emphasized by De Giorgi et al. and Dika et al. These authors highlight that recognizing the specific features of each lesion type can aid in the appropriate pathological assessment and management of patients [10, 11].

Spitzoid lesions encompass a wide range of melanocytic neoplasms, including benign Spitz nevi, atypical Spitz tumors (ASTs), and malignant spitzoid melanomas, all of which present significant diagnostic challenges. The overlapping histopathological features often lead to the identification of ASTs by exclusion. Spitz nevi typically appear as small, symmetric, well-defined lesions characterized by uniform cellularity and minimal atypia, with any mitotic activity confined to the superficial dermis. In contrast, ASTs exhibit several intermediate characteristics, including asymmetry, mild to moderate cytological atypia, increased cellularity, and deeper mitotic figures, but lack the extensive invasion seen in melanomas. On the other hand, spitzoid melanomas are marked by pronounced asymmetry, significant atypia, high mitotic rates, and an invasive growth pattern, placing them at a considerably higher risk of metastasis. These distinguishing features are essential for accurately

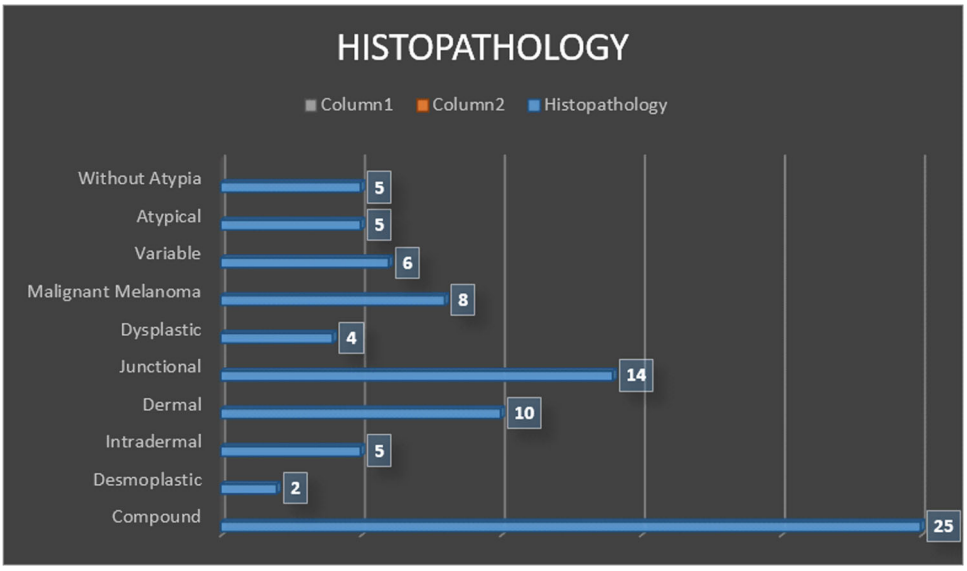

FIGURE 1 | Prevalence of patients based on site of involvement.

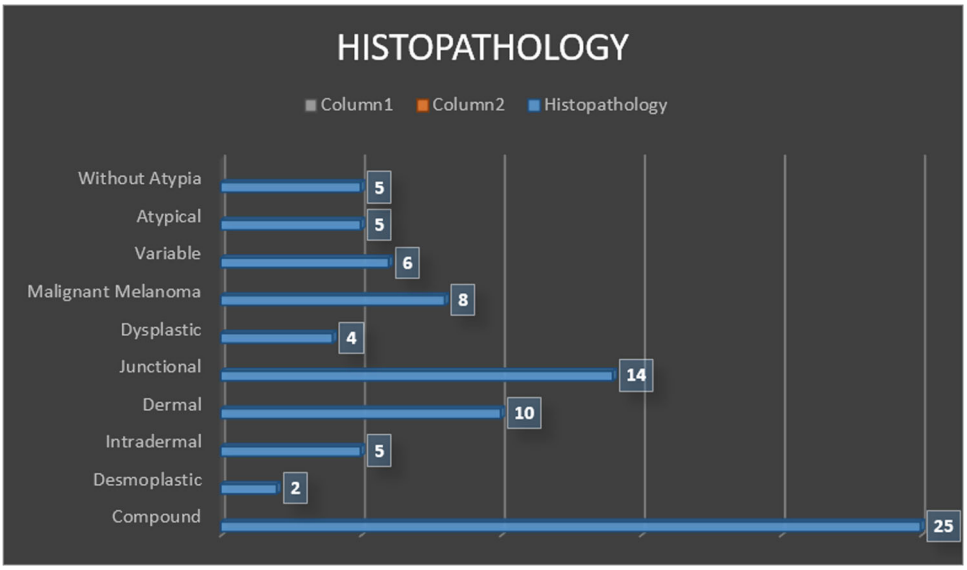

FIGURE 2 | Prevalence of patients based on histological characteristics of lesions.

TABLE 1 | Frequency of patients based on histopathological characteristics of lesions.

Histopathology	Frequency (%)
Compound Spitz nevus	25 (29.4)
Desmoplastic Spitz nevus	2 (2.4)
Intradermal Spitz nevus	5 (5.9)
Dermal Spitz nevus	10 (11.8)
Junctional Spitz nevus	14 (16.5)
Dysplastic Spitz nevus	4 (4.7)
Malignant melanoma	8 (9.4)
Variable	6 (7.1)
Without atypia	5 (5.9)
Atypical	5 (5.9)
Inconclusive	1 (1.2)

categorizing each lesion and ultimately guiding appropriate clinical management (Table 2).

The distribution of lesions predominantly on the upper extremities and face corresponds with observations made by Dika et al., who noted diverse clinical and dermatoscopic features in Spitz nevi among children, emphasizing the common facial involvement [12]. Similarly, our study's most common histopathological types—compound, junctional, and dermal Spitz nevus—align with the known heterogeneity of these lesions, as discussed by Broganelli et al. [13], who reported a wide spectrum of Spitzoid tumors [13].

Interestingly, the disease duration observed in our study primarily spanned less than 2 years, with significant occurrences within the first and second years. This finding suggests a tendency for earlier presentation or diagnosis, which might be due to increased awareness or the readily visible nature of the lesions, especially given their common facial location. Costa et al. also highlight the importance of distinguishing Spitz nevi from melanoma, particularly when lesions appear symmetrical, underscoring the critical role of timely and accurate diagnosis [14].

The histopathological findings of this study, particularly the prevalence of compound Spitz nevus (29.4%), followed by junctional (16.5%) and dermal Spitz nevus (11.8%), align with the recognized diversity in Spitzoid lesions. These findings are in harmony with the observations made by Broganelli et al., who documented a broad spectrum of Spitzoid tumors, reflecting the heterogeneity of these lesions [13]. This spectrum is significant as it underscores the variability and complexity in diagnosing and managing these lesions. While our study presents a higher prevalence of compound Spitz nevus, similar trends are noted in other regions, indicating a possible commonality in the histopathological presentation of Spitz nevus. However, it's crucial to consider geographical and ethnic variations that might influence these findings, as seen in a recent study by Rousi et al., where an increased incidence of melanoma necessitates a careful pathological review to distinguish it from Spitzoid lesions [15]. Raghavan et al. discussed a unique presentation of eruptive Spitz nevi, highlighting the potential for these lesions to exhibit benign metastatic behaviors, further complicating the diagnostic landscape and demonstrating the unpredictable nature of Spitzoid lesions [16] (Table 3).

The emphasis on differentiating Spitz nevus from melanoma, as discussed by Costa et al., further supports the need for meticulous histopathological examination to ensure accurate diagnosis and appropriate management of these lesions [14]. Therefore, while our study adds valuable data to the existing knowledge, it also reinforces the necessity for continued comparative and collaborative research to refine the understanding of Spitz nevus' histopathology across different populations.

Our study did not find any underlying diseases associated with Spitz nevus, which supports the notion that these are primarily isolated occurrences rather than manifestations of broader

TABLE 2 | The differential diagnosis of spitzoid lesions [10, 11].

Feature	Benign Spitz nevus	Atypical Spitz tumor (AST)	Malignant Spitzoid melanoma
Size	Small (< 1 cm)	Variable (van be large)	Variable (often > 1 cm)
Symmetry	Symmetric	Asymmetric	Marked asymmetry
Circumscription	Well-circumscribed	Ill-defined or poorly circumscribed	Poorly defined
Cellularity	Uniform cellularity	Increased cellularity	High cellularity
Cytologic Atypia	Minimal atypia	Mild to moderate atypia	Prominent atypia
Mitosis	Rare, if present, confined to the superficial dermis	Deeper mitotic figures (maybe present)	High mitotic activity
Invasion	Non-invasive	Non-invasive	Invasive
Metastatic Potential	Very low risk	Uncertain (depends on features)	High risk
Histopathological Features	Nevoid structure, often nested	Intermediate features may mimic melanoma	Infiltrative growth, necrosis, and ulceration are possible

TABLE 3 | Histopathological features of classic Spitz nevi versus atypical Spitz tumors [16].

Indicators	Classic Spitz nevus	Atypical Spitz tumor
Structure	Orderly, nondisruptive	Haphazard, infiltrative
	Symmetrical	Asymmetrical
	Sharply demarcated	Poorly circumscribed
	Intact, hyperplastic epidermis	Disrupted, ulcerated epidermis
	Aggregates of Kamino bodies	Absent or few Kamino bodies
	Junctional clefting	Lack of junctional clefting
	Lack of deep involvement	Subcutaneous involvement
	Limited pagetoid spread, lower epidermis	Prominent, single-cell pagetoid spread, beyond epidermal nests
	Diminished cellularity with depth	Confluence, dense cellularity
	Zonation: side-to-side uniformity	Lack of zonation
	Smaller nests with depth	Persistent, expansile deep nests
Proliferation	Mitoses $< 2/mm^2$	Mitoses $\geq 2–6/mm^2$
Cytology	Spindled or epithelioid cell type	More heterogeneous cell types
	Ground glass or opaque cytoplasm	Granular, dusty cytoplasm
	Low nuclear-to-cytoplasmic ratio	High nuclear-to-cytoplasmic ratio
	Delicate, dispersed chromatin	Hyperchromatism
	Uniform nucleoli	Large, eosinophilic nucleoli

systemic issues. However, Rousi et al. note an increased incidence of melanoma in children and adolescents in Finland [15], indicating the necessity of careful differentiation between Spitz nevus and more pathologies like melanoma.

The conclusion of this study calls for further research incorporating molecular analyses and enhanced clinical evaluation techniques, a sentiment echoed by Afanasiev et al. and Laar et al., who explore the translation of melanoma biomarkers into solid tissue assays to improve diagnostic accuracy [17, 18]. Such advancements could be particularly beneficial in the diagnosis and understanding of Spitz nevus, potentially leading to more personalized and precise care.

In summary, while our study provides a detailed look at the demographics, clinical presentation, and histopathology of Spitz nevus in a specific population, it also highlights the need for continued research and innovation in diagnostic techniques. The variations and similarities with other studies reflect the complex nature of Spitz nevus and the ongoing quest for clarity in its diagnosis and management.

5 | Conclusion

This retrospective study offers valuable insights into the demographics, clinical features, and histopathology of patients

with Spitz nevus, revealing a slight female predominance, a young average age of presentation, and a preference for the upper extremities and face. The findings highlight the histopathological diversity, with compound Spitz nevus being the most common type, emphasizing the need for precise diagnosis and differentiation from malignant pathologies like melanoma. The study underscores the importance of further research, including molecular and immunohistochemical analyses, to enhance understanding and management of Spitz nevus, contributing to the broader dermatological knowledge and advocating for more in-depth, collaborative investigations.

Author Contributions

Zeinab Aryanian: conceptualization, investigation, supervision. **Kambiz Kamyab:** investigation, writing–original draft, methodology. **Safoura Shakoei:** investigation, methodology. **Ifa Etesami:** validation, visualization, writing–review and editing. **Vahidehsadat Azhari:** investigation, writing–review and editing. **Sami Hesami:** project administration, formal analysis. **Azadeh Khayyat:** data curation, software. **Parvaneh Hatami:** methodology, writing–review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Transparency Statement

The lead author Sami Hesami, Azadeh Khayyat, Parvaneh Hatami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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