Ambiguity and Lymphatic Penchant-Spitzoid Neoplasm

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Abstract

Sophie Spitz initially scripted the specific melanocytic neoplasm in 1948 as "juvenile melanomas" or as "melanoma of childhood". Spitz nevi are enunciated as benign melanocytic neoplasm preponderantly occurring in the paediatric age group although adults are also incriminated [1].

Spitzoid neoplasm is infrequently occurring melanocytic lesions of children or adolescents which constitute an estimated 1% of surgically resected melanocytic neoplasm. Reed nevus is designated as the pigmented variant of Spitz nevus with an identical morphology and evolution, frequently exemplified on lower extremities.

Keywords: Ambiguity; Lymphatic Penchant; Spitzoid Tumour

Abbreviations: MST: Malignant Spitz Tumour; AST: Atypical Spitz Tumour; STUMP: Spitzoid Tumour of Unknown Malignant Potential; MELTUMP: Melanocytic Lesions of Uncertain Malignant Potential; SAMPUS: Superficial Atypical Melanocytic Proliferation of Uncertain Significance.

Introduction

Disease Characteristics

Spitzoid neoplasm depicts lymphotropic properties with a propensity to invade local and regional lymph nodes. Spitz melanoma or malignant Spitz tumour (MST) is a nomenclature utilized for Spitzoid neoplasm depicting marked cellular and nuclear atypia and an aggressive clinical course resulting in distant metastasis and death. Spitzoid melanocytic neoplasm demonstrates histology betwixt Spitz nevus and malignant Spitz tumour. It can be challenging to predict the biological potential and clinical outcome of ambiguous morphologies [1,2].

Spitzoid neoplasm can be misdiagnosed as a Spitz nevus or malignant Spitz tumour. Spitzoid neoplasm also bear the nomenclature of atypical Spitz tumour (AST), Spitzoid tumour of unknown malignant potential (STUMP), melanocytic lesions of uncertain malignant potential (MELTUMP), superficial atypical melanocytic proliferation of uncertain significance (SAMPUS), dysplastic Spitzoid neoplasm or borderline Spitzoid neoplasm. Additionally, ambiguous non Spitzoid melanocytic neoplasm can be included in the terminology of melanocytic lesions of uncertain malignant potential (MELTUMP) and superficial atypical melanocytic proliferation of uncertain significance (SAMPUS) [2,3].

Clinical Elucidation

Emergence of a solitary, brisk, pink, red or brown papule upon the face and extremities is observed. Spitz nevus is frequently delineated as nodules on the trunk, lower extremities or ventral torso. Lesions on the tongue are accompanied by pseudo-epitheliomatous hyperplasia of the superimposed squamous epithelium and can recapitulate a malignant condition. Spitzoid neoplasm can enunciate miniature, elevated, pinkish red or brownish black nodules which clinically resemble a haemangioma

or a pyogenic granuloma. Magnitude of the lesion is usually 6 millimetres or below.

Lesions of Spitzoid neoplasm are generally singular. However, multiple and aggregated or multiple and disseminated nodules can be cogitated. Spitz nevi are commonly benign lesions although can reoccur with incomplete eradication. Atypical Spitzoid neoplasm can incriminate several regional lymph nodes with nodal metastasis [2,3].

Histological Elucidation

Spitzoid neoplasm displays a distinct architecture and is comprised of enlarged epitheloid or spindle shaped melanocytes encompassing enlarged nuclei with vesicular chromatin and prominent nucleoli.

A cogent diagnosis of Spitzoid neoplasm can be obtained on an appropriate histology and necessitates the incorporation of contextual clinical features, especially patient's age, as lesions in adults exhibit a higher percentage of malignant conversion. Spitzoid neoplasm can emerge as compound, intradermal or junctional lesion. Intradermal location is frequently cogitated in adults. Spitzoid neoplasm display a characteristic population of enlarged epitheloid cells or spindle shaped melanocytes or an admixture of dual cell population [3,4].

Spitz nevus generally exceeds > 5 millimetres magnitude and depicts a dome or wedge shaped, symmetrical, well circumscribed perimeter. Cellular maturation and zonation extends within the depth of lesion and epidermal hyperplasia is cogitated. Superficial ulceration, absent or minimal mitosis, cytological with nuclear atypia and lack of subcutaneous tissue infiltration are cogent features.

Cellular zonation is manifest in benign Spitz nevus with the appearance of enlarged cells within superficial epidermal layers and sequential maturation of melanocytes originating from extraneous surface of the lesion to deep dermal regions with a decline in quantifiable cell nests, cellular dimensions, nuclei and nucleoli. However, atypical or malignant counterparts may lack aforesaid characteristics of zonation and cellular maturation [3,4].

Spitzoid neoplasm variably demonstrates cellular and nuclear maturation. Disbursement of melanin pigment can be zone specific or confined subjacent to the epidermis.

Kamino bodies are a characteristic histological feature of Spitzoid neoplasm and indicate benignancy. On ultra-structural analysis, Kamino bodies are constituted of amorphous filaments and basement membrane components such as collagen types IV, VII and laminin. Apoptosis of singular cells is absent. Kamino bodies require a distinction from Civatte or colloid bodies, commonly elucidated in lichen planus and adjunctive dermatoses. Superior epidermal extension of singular melanocytes is infrequent in Spitzoid neoplasm, in contrast to conventional malignant melanoma. Pagetoid extension of Spitzoid cells, if discerned, occurs in bundles or discrete cells nests.

Fascicles of Spitzoid cells demonstrate a vertical orientation, are devoid of cohesion and configure retraction spaces from adjoining epidermis in order to recapitulate a "bundle of bananas" or a "rain down" pattern. Aforesaid morphological attributes are elucidated at the dermo-epidermal junction and are frequent in Spitzoid neoplasm, in contrast to malignant melanoma [4,5].
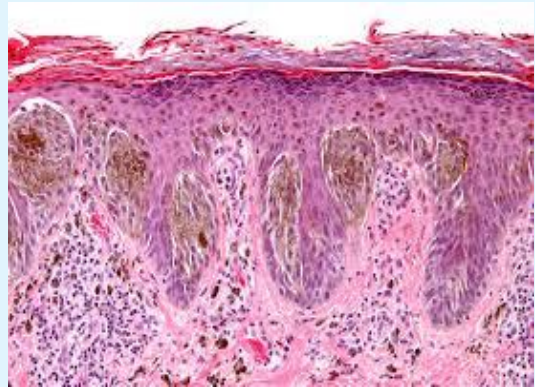
Spitz nevus exhibits "adnexotropism" on account of incrimination of hair follicles and eccrine ducts with the Spitzoid cells. Dissemination of inflammatory infiltrate in Spitz nevus is perivascular and diffuse amidst collagenous bundles, in contrast to Spitzoid malignant melanoma where the inflammatory infiltrate abounds at the base of the lesions.

Atypical Spitzoid neoplasm are indicative of an intermediate histology amidst Spitz nevus and malignant Spitz tumour. Atypical Spitzoid tumours depict a suspicious histology with the enunciation of a singular or more parameters, configured as tumour ulceration, tumour magnitude beyond > 5 centimetres, tumour infiltration into subcutaneous tissue with "pushing" margins, enhanced cytological and nuclear atypia, augmented cellular density with tumour confluence, dermal mitosis exceeding > 2/high power fields, absence of junctional clefts, absent or minimal Kamino bodies and an extensive pagetoid spread of the tumour.
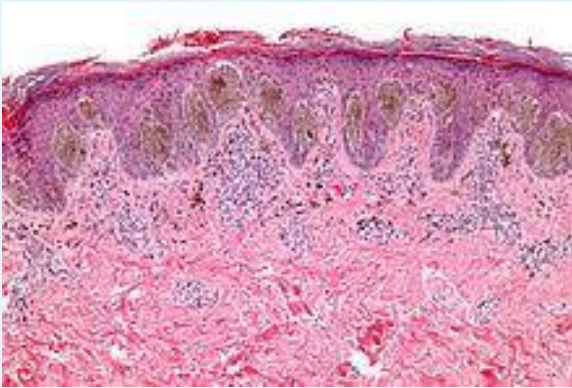
Malignant Spitz tumour displays cogent and diagnostic histological criterion such as superficial ulceration, asymmetrical architecture, infiltrative pattern of tumour progression, severe and/or confluent cytological and nuclear atypia, dermal mitosis, "pushing" tumour margins, effacement of superficial epidermis and pagetoid pattern of tumour extension [4,5] (Figure 1-12).
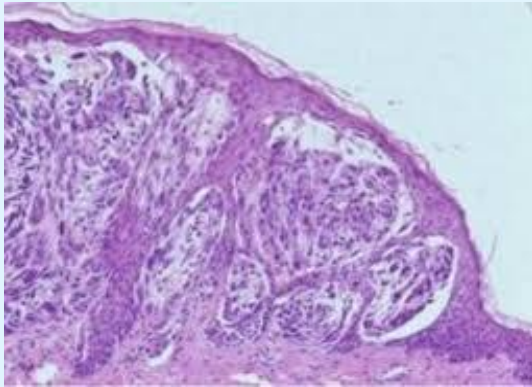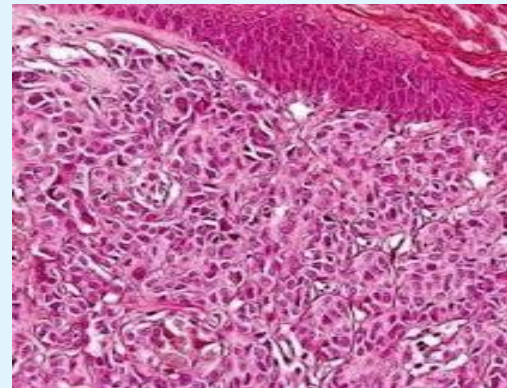
Figure 1: Spitz neoplasm with intradermal epitheloid and spindle cell component and attenuated superficial epidermis [6].
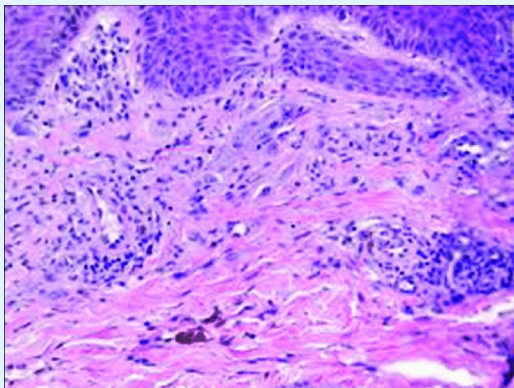

Figure 2: Spitz nevus with upper dermal aggregates of pigmented, epitheloid cells, stretched out epithelium with hyperkeratosis [7].

Figure 3: Spitz nevus with intradermal clusters and dissemination of epitheloid to spindle shaped cells [8].

Figure 4: Spitz nevus with epitheloid cell dispersion, pigmented melanocytes and epidermal hyperplasia [9].

Figure 5: Spitzoid neoplasm with atypical melanocytes, enlargement, hyperchromasia, pigmentation, nucleolar prominence and dermal dispersion with junctional activity [10].
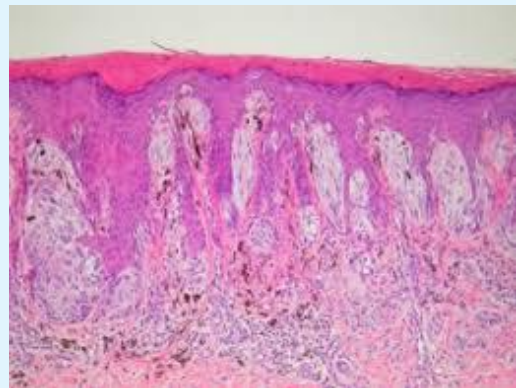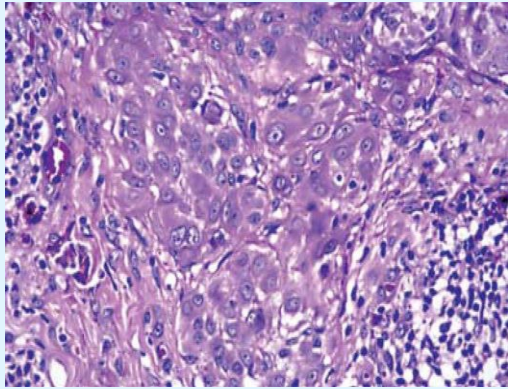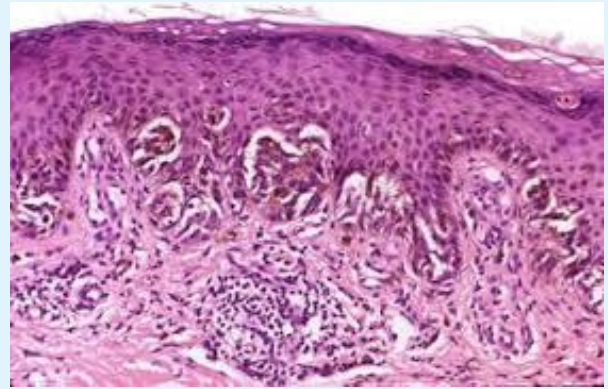

Figure 6: Spitz neoplasm with epidermal prominence, dermal epitheloid and spindle cell clusters with mild infiltrate at the dermal-epidermal junction [11].

Figure 7: Spitzoid neoplasm with anisocoria, carinomegaly, atypical melanocytes with vesicular nuclei and prominent nucleoli [12].

Figure 10: Spitzoid neoplasm with junctional activity, pigmentation, intradermal aggregates and epidermal prominence [14].
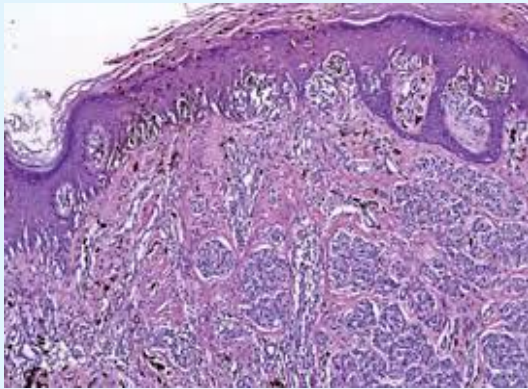
Figure 8: Spitoid neoplasm with a dense dermal exudation of atypical melanocytes, significant invasion of the dermal-epidermal junction, pigmented cell clusters and epidermal enhancement [12].
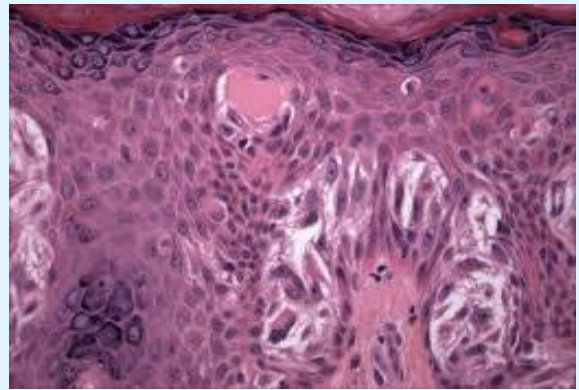
Figure 11: Spitz nevus with epidermal hyperplasia and epitheloid and spindle cell clusters abutting the dermal- epidermal junction [14].
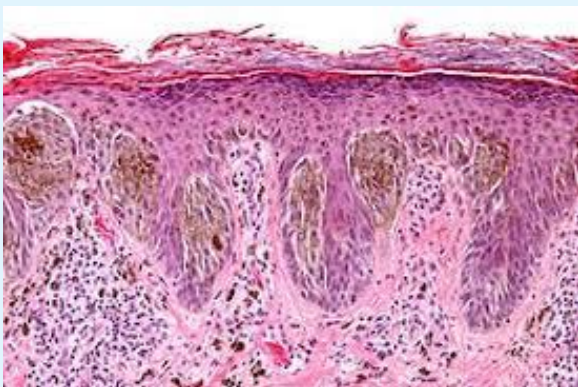
Figure 9: Spitzoid neoplasm, with pigmented melanocytes, epitheloid cell nests, moderation infiltration of the dermal- epidermal junction and hyperplasia of superficial epidermis [13].
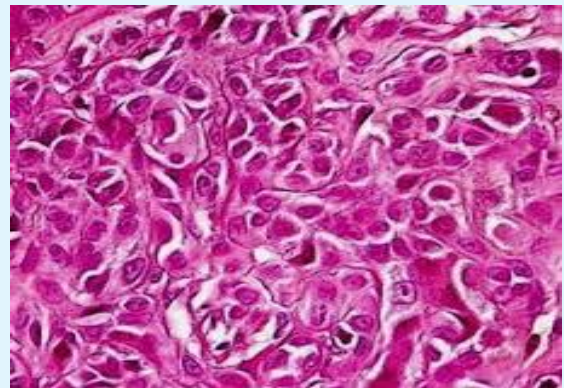
Figure 12: Spitz nevus with atypical epitheloid and spindle cell nests with nuclear and cellular pleomorphism and nuclear hyperchromasia [15].

Immune-Histochemical Elucidation

As histological attributes necessary to differentiate atypical Spitzoid tumour from Spitz nevus or Spitzoid malignant melanoma are indeterminate, evaluation of ambiguous Spitzoid neoplasm requires the application of ancillary techniques such as immune histochemistry and molecular pathology. Immune reactivity of nuclear proteins MIB-1/Ki-67 are frequently employed and are amplified by tumour cells within active phase of cell cycle. Immune expression of MIB-1/Ki-67 in Spitz nevus is predominantly confined to superficial portion, whereas expression of MIB-1/Ki-67 in malignant Spitz tumour is amplified and depicted within the superficial segment and depth of the lesion [5,16].

Immune reactivity to phosphohistone-H3 (PHH3) indicates mitotic activity which is sparse on account of restricted PHH3 expression within mitotic figures emerging from early prophase through metaphase, anaphase and telophase. In contrast, immune reactivity to MIB-1/Ki-67 is cogitated within the entire replicative cell cycle including G1 and G2 phase.

Elucidation of Cyclin D1 is enhanced in Spitzoid neoplasm although it is devoid of concurrence with cellular proliferation. Thus, immune reactivity for Cyclin D1 is not recommended in assessment of Spitzoid neoplasm. Melanocytic markers can be evaluated in Spiztoid neoplasm.

Immune reactivity for HMB-45 depicts a cytoplasmic staining with declining intensity within the depth of a Spitz nevus. Immune reactivity of HMB-45 within a malignant Spitz tumour is uniform and comprehensive throughout the lesion [2,3]. Immune molecule S-100 is diffusely expressed in Spitzoid neoplasm and is independent of benign or malignant nature of the lesion. Thus, a differentiation of ambiguous Spitzoid lesion may not be possible with the application of S-100. However, a subtype of S-100 protein, cogitated as S100A6 can be employed to segregate Spitz nevus from malignant Spitz tumour. Immune reactivity for S-100A6 is intense in Spitz nevus and reduced in malignant Spitz tumour [16,17].

Molecular Elucidation Molecular aberrations in Spitzoid neoplasm include mutation of HRAS, particularly Q61/K/R in exon 3. BRAFV600E is persistently detected with preceding BAP1 inactivating germ-line mutations along with prominent genomic rearrangements of the ALK, NTRK1, RET, ROS1, METRTKs or BRAF serine threonine kinase. Aforesaid mutations control the evolution of benign Spitz nevus and represent preliminary genetic modifications triggering the exemplification of metastatic melanoma [2,3].

Concurrence of mitogen activated protein kinase/extracellular signal- regulated kinases (MAPK/.ERK) and phosphoinositide 3-kinase/ protein kinase B/ mammalian target of rapamycin (PI3K/AKT/ m TOR) pathway enhance cellular proliferation in Spitz nevus with a consequent initial, expeditious progression of the lesion. Subsequently, diverse tumour suppressive methodologies activate the p53 and p16 cascade and prevent further tumour progression. Damage response mechanism of DNA such as telomere shortening and emergence of reactive oxygen species (ROS) mobilize the MAPK/ERK cascade. PI3k/AKT/ m TOR pathway is genetically triggered through de-repression of CDKN2A genetic locus in concordance with activation of oncogenic pathways. Repudiation of tumour suppressor mechanisms incurs cellular proliferation and progression of atypical Spitzoid tumours [2,3].

Additional genetic aberrations initiate the emergence of aggressive malignant Spitzoid neoplasm such as genetic mutations within PTEN and ARID2A genes along with the TERT promoter region. Spitzoid melanocytic neoplasm are subcategorized into three distinct groups contingent to discernible genetic alterations. Majority of tumours enunciate a kinase fusion of ALK, ROS1, NTRK1, BRAF, RET, MET genes which are infrequent in adjunctive subtypes of melanocytic neoplasm [17,18].

Additional subgroups are composed of subjects displaying the HRAS or BAP1 genetic mutation. Aforesaid genomic aberrations display a characteristic histological phenotype. Spitz nevi with HRAS mutation is accompanied with significant desmoplasia (desmoplastic Spitz nevus). Lesions with BAP1 mutation enunciate epithelia morphology.

Elucidation of copy number variations (CNV) is a significant factor in assessing tumour risk, suitability of surgical and systemic approaches of tumour management and prognostic outcomes. Diagnostic modalities such as comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH) are cogent in deciding probability of malignant transformation in ambiguous or atypical Spitzoid neoplasm. Common chromosomal copy number variation (CNV) are elucidated such as copy number gains in chromosome 1q,6p,7, 8q,17q with 20q and copy number deletions in chromosome 6q, 8p, 9p with 10q along with concordant clinical behaviour as demonstrated by the neoplasm. Copy number gains of

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6p25 or 11q13 and a homozygous deletion in 9p21 depict aggressiveness in an atypical Spitzoid neoplasm [2,3].

Homozygous chromosomal deletion of 9p21 is frequently recognized in juvenile atypical Spitzoid neoplasm. Aforesaid Spitzoid neoplasm display an epitheloid cell morphology, extensive and nodular tumour progression, atypical mitosis in deep-seated dermal tumour, homozygous 9p21 deletion in a majority of cells, absent elucidation of immune reactive p16 protein and BRAF mutations in a minority of neoplasm with consequent nodal metastasis within in- transit, adjunctive and non-sentinel lymph nodes [17,18].

However, incrimination of sentinel lymph nodes in an atypical Spitzoid neoplasm is not an indicator of tumour aggression. It is also not contemplated as a preferred diagnostic procedure in lesions of juvenile or adult subjects.

Atypical Spitzoid tumours delineating 6q23 chromosomal deletion are minimally aggressive, can incriminate sentinel lymph nodes and infrequently demonstrate distant metastasis.

Notwithstanding, a diagnostic algorithm for categorizing and evaluating probable malignant progression of atypical Spitzoid tumours necessitates the adoption of appropriate immune histochemical markers and molecular assays. Apart from pertinent histological correlation, elucidation of immune reactive p16ink4a, dual colour Ki67, MART-1 and HMB-45 along with five probe fluorescent in situ hybridization (FISH) protocol indicating 6p25,8q24,11q13,CEN9 and 9p21 chromosomes besides an array based comparative genomic hybridization (array-CGH) panel is a cogent, distinguishing selection. Aforesaid diagnostic algorithm is contemplated as an evolution in the management of ambiguous, atypical melanocytic tumours [2,3].

Molecular-Histological

Concurrence Majority of Spitz nevi demonstrate a normal karyotype on array CGH. Singular gain in chromosome 11p at the position of HRAS locus is cogitated in an estimated 20% Spitz nevi. Genetic mutations of HRAS depict significant cellular proliferation sequential to a protein trigger through activation of MAPK and PI3K/AKT/m TOR pathways.

Spitz nevi with HRAS mutations depict specific cytological features such as a preponderantly intradermal tumour component with a prominent, desmoplastic stroma and reduced tumour cellularity. Melanocytes are enlarged and exhibit pleomorphic nuclei. Spitz nevi with HRAS mutation exemplify tumour infiltration at the base, minimal to absent melanin pigment and singular cell extension amidst collagen bundles. Additionally, mitosis are deep seated and appear within the inferior portion and/or base of the lesion. Aforesaid manifestations are particularly prominent in lesions of the elderly. HRAS mutation indicates a benign Spitz nevus accompanied by a superior clinical outcome [2,3].

Genetic mutations of RAS genes are singularly inadequate in inducing tumour-genesis and require concurrence of additional genetic manifestations such as BRAF mutations or inactivation of p16 or p53 in order to stimulate malignant conversion. Notwithstanding, evaluation of HRAS mutations is beneficial in differentiating Spitz nevus from Spiztoid melanoma [18,19].

Bi-allelic chromosomal depletion of BAP1 gene is associated with epitheloid melanocytic tumours which preponderantly emerge in the sun exposed skin. Cutaneous melanocytic tumours are innumerable and characteristically arise as enlarged, skin coloured papules or nodules of 5 millimetre to 10 millimetre magnitude, frequently intradermal with incrimination of the dermal-epidermal junction.

Plump epitheloid cells enunciate a well-defined cytoplasmic outline, amphophilic cytoplasm, enlarged, round to oval nuclei with vesicular chromatin and variable, prominent nucleoli. The cellular congregate is admixed with multinucleated giant cells and can depict a miniature component of a peripheral nevus. Tumour infiltrating lymphocytes (TIL) are abundant [18,19].

Lesions are devoid of characteristic features of Spitz nevus such as clefts surrounding nevoid nests at the dermo-epidermal junction, spindle shaped melanocytes, hyperplasia of the superimposed epidermis, hyper-granulosis and enunciation of Kamino bodies. A subset of tumours depicts aberrant features such as nuclear pleomorphism, enhanced cellularity and augmented mitotic figures which may label the neoplasm as ambiguous.

Bi-allelic deletion of BAP1 gene is interstitial and implicates a portion of chromosome 3p. Atypical Spitzoid lesions with genetic deletion of BAP1 contain BRAF V600E mutation which are also elucidated in common nevus and Spitzoid neoplasm. BRAF V600E protein can be discerned by immune reactive staining. Thus, it can be

surmised on molecular assay and histological enunciation that lesions demonstrating BAP1 chromosomal deletion are not true Spitz nevi [2,3].

Fusion of anaplastic lymphoma kinase (ALK) gene is cogitated in 8% of Spitz nevus, 5% of atypical Spitzoid tumour and 1% of Spitzoid melanoma. Neoplasms with ALK fusion are enunciated in younger individuals, in contrast to elderly subjects devoid of the particular chromosomal translocation. Specific Spitz tumours are dome shaped or exophytic and predominantly arise in the extremities. Majority of aforesaid tumours are amelanotic or can depict excessive pigmentation. Spitzoid neoplasm immune reactive to anaplastic lymphoma kinases (ALK) are compound and demonstrate a plexiform pattern of tumour evolution. Enlarged aggregates of fusiform to polygonal melanocytes delineate anarchitecture of elongated, radial or vertical cellular nests, a bulk of which exemplify prominently infiltrative tumour progression with deep-seated foci of dermal invasion. Mitotic figures can be frequently cogitated within the dermis. Melanocytes within the neoplasm are devoid of prominent pleomorphism and exhibit an amphophilic, fibrillary cytoplasm and enlarged nuclei with prominent nucleoli. Spitz tumours enunciating fusion of ALK genes can be appropriately discerned with immune histochemistry [2,3].

Genetic translocation of anaplastic lymphoma kinase (ALK) can be demonstrated with fluorescent in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT- PCR) or next generation sequencing.

Spitz neoplasm with ALK translocations necessitate a segregation from conditions such as irritated melanocytic nevi, virus induced verrucae or molluscum contagiosum or vascular malformations represented by angioma or pyogenic granuloma [19,20].

Genetic fusion of ROS1 gene is the second frequent aberration in Spitz nevus and is elucidated in approximately 10% instances. Spitz tumours contingent to ROS1 genetic fusion are dome shaped, well circumscribed, compound melanocytic tumours. Aforesaid lesions comprise of enlarged, spindle shaped and epitheloid melanocytes demonstrating variable atypia and vesicular nuclei accompanied by inconstant hyperplasia of the superimposed epithelium and Kamino bodies.

Immune histochemical elucidation with anti ROS1 antibody can assist the discernment of aforesaid lesions. Fluorescent in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR) and next generation sequencing additionally delineate aberrant Spitzoid neoplasm. Genetic fusion and signalling mechanisms of ROS1 are concurrent with primordial signalling pathways such as MAPK/ ERK and PI3K/AKT/m TOR [2,3].

Genomic fusion of NTRK1 genes are discerned in around 10% Spitzoid neoplasm. Tumours with aforesaid genetic aberrations depict clinical attributes of classic Spitzoid neoplasm in the absence of a characteristic histology. Intertwining fascicles of fusiform melanocytes are infrequently cogitated within the dermis, in contrast to ALK + tumours. Intense immune staining of NTRK1 molecule aids detection of the particular anomaly [2,3]. NTRK3 protein belongs to Trk family of neurotrophin receptors which enunciates a reaction as a trans-membrane tyrosine kinase receptor to neurotrophins. Spitzoid neoplasm displaying NTRK3 genetic fusion are delineated in young individuals below 18 years of age. Spitzoid pattern of tumour evolution is indeterminate along with appearance of specific features such as incrimination of the dermis by enlarged aggregates of epitheloid to spindle shaped melanocytes displaying enhanced cytoplasm, in contrast to miniature melanocytes populating conventional nevi [2,3].

Genetic rearrangements of RET gene are infrequently cogitated in beneath < 5% Spitzoid neoplasm. Aberrations of RET gene activate the common signalling pathways of MAPK/ERK and PI3K/AKT/m TOR along with mobilized PLCγ-1 pathway. Therapeutic administration of RET inhibitors prohibit oncogenic potential of Spitzoid neoplasm [2,3]. Identically, genetic rearrangements of MET gene are exceptional and activate MAPK/ERK and PI3K/AKT/m TOR signalling pathway. Genomic mutation of TERT promoter region is frequent in Spitzoid neoplasm with the incurrence of haematogenous tumour metastasis. Thus, TERT aberrations are contemplated as a potential biomarker of aggressive behavior [2,3].

Investigative Profile

On dermoscopic evaluation, definitive configurations are elucidated. "Globular" articulations are enunciated in Spitz nevus whereas "starburst" pattern is exemplified in Reed nevus. Adjunctive dermoscopic arrangements are infrequent such as the "homogeneous black pattern", "homogeneous pink pattern" with classical dotted or irregular vasculature and the "inverse network pattern". Interwoven, hypo-pigmented serpiginous or linear articulations configure a network which circumscribes irregular, pigmented, globular arrangements or dotted

blood vessels. Associated crystalline or chrysalis structure is the hallmark of inverse network pattern [4].

An estimated one fifth (20%) instances of Spitz nevus exhibit a "multicomponent" or "atypical pattern" with an asymmetric dissemination of characteristic structures, colours and pigmented configurations akin to a "white blue veil". Asymmetric evolution of Spitz nevus is contemplated as an indicator of morphological atypia. Spitz nevi frequently delineate the starburst, globular and multicomponent dermoscopic arrangements with sequential reticular/ homogeneous and the inverse network pattern.

Specific histological patterns are associated with cogent dermoscopic arrangements. Globular pattern on dermoscopy is enunciated in the classic- desmoplastic variant of Spitz nevus. Similarly, starburst pattern is typically demonstrated in pigmented Spitz nevus, Reed nevus and Spitz/Reed nevus. Multicomponent pattern is manifested in Spitz nevi delineating histological atypia [4].

Therapeutic Options

Paediatric Spitzoid neoplasm are appropriately managed by conservative approach. Close monitoring of the lesion is necessitated in order to discern the emergence of Spitzoid melanoma. Spitz nevus can appear to be of uniform morphology and miniature at initial discernment although can display excessive growth or irregular configuration during subsequent monitoring. Three to six month interval is considered as an optimal period for suitable follow up. Enhanced magnitude beyond 8 millimetres, unstable lesions with classic emergence of globules of varying magnitude and hues/colour or the observation of expansive growth with divergent morphological attributes during monitoring is aptly addressed by a comprehensive surgical excision of the Spitzoid neoplasm [20,21].

Pre-adolescents or children beneath 12 years of age displaying typical Spitz nevus mandate a close supervision for 6 months to 12 months for the enunciation of stable, homogeneous lesions on dermoscopy and a gradual involution. Stable nevi which do not involute can be exterminated surgically contingent to factors such as individual compliance to surgery, aesthetic outcomes along with psychological and social impact. Spitzoid neoplasm of uncertain malignant potential (STUMP) are appropriately managed with a comprehensive surgical elimination. Evaluation of sentinel lymph node may not be necessitated, however, a regular clinical evaluation is advisable [21,22].

Spitz Nevus		Atypical Spitz Tumour	Malignant Spitz Tumour/ Melanoma
Clinical	Features		
Patient Age	Usually <20 yrs	All ages>10yrs	All ages>10yrs
Location	Face, limbs, neck/Universal	Universal	Universal
Architectural	Pattern		
Diameter	<5mm	>5mm	Often>10mm
Outline	Dome, wedge, symmetric	Asymmetrical	Asymmetrical
Circumscription	Sharp	Often poor	Poor
Epidermal hyperplasia	Present	Epidermal effacement	Absent or epidermal effacement
Maturation with dermal depth and zonation	Present	Uncommon, absent	Usually absent
Subcutaneous ingress	Orderly at the deep margin	Frequent extension with "pushing margin"	Deep, irregular extension with infiltrative growth
Cellular	Morphology		
Cell type	Uniform spindle or epitheloid	Spindle or epitheloid with increasing atypia	Spindle or epitheloid with atypia and pleomorphism
Cytoplasm	Opaque/ground glass	Granular	Granular/mixed
Nuclei/Nucleoli	Open, delicate chromatin, uniform nucleoli	Heterogeneous chromatin, prominent nucleoli	Absent chromatin pattern, hyperchromasia, large nucleoli
N/C ratio	Low	Increasing	High
Pigment	Superficial distribution	Variable	Variable, deep, irregular
Proliferative	Activity		
Mitotic rate	Absent or rare ,<2/sq mm, no	2-6sq mm. Deep or	2-6sq mm. Deep or marginal

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	atypical mitosis	marginal dermal mitosis may appear.	dermal mitosis frequent.
Proliferative index (Ki67 /MIB-1)	<2%	2%-10%	>10%
Adjunctive	Diagnostic	Features	
Ulceration	Absent	Often	Frequent
Kamino Bodies	Present	Absent or few	Typically absent
Host response	Inconspicuous	Fibroplasia, patchy lymphocytic infiltrate in papillary dermis	Band like-patchy mononuclear lymphocytic infiltrate
Associated Features	Junctional clefts, telangiectasia, transepidermal elimination of cell nests		

Table 1: Histology of Spitzoid Neoplasm [2].

Molecular alteration	Spitz nevus	Atypical Spitz tumour	Spitzoid malignant melanoma
NRAS	0%-5%	0%-25%	0%-25%
HRAS	15%-20%	14%	0%
BRAF	0%-20%	0%-25%	0%-25%
BAP1		15%	
CDKN2a		Deletion of 9p21 (homozygous>heterozygous)	
Kit Fusions	55%	56%	39%
ALK	8%	5%	1%

Table 2: Molecular alterations in Spitzoid Neoplasm [3].

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7. Image 2 Courtesy: Wikipedia.

8. Image 3 Courtesy: Research gate.

9. Image 4 Courtesy: Wikimedia commons.

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