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Clinical, Morphologic and Genomic Findings in *ROS1* Fusion Spitz Neoplasms.

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Abstract

The presence of a characteristic chimeric fusion as the initiating genomic event is one defining feature of Spitz neoplasms. Characterization of specific subtypes of Spitz neoplasms allows for better recognition facilitating diagnosis. Data on clinical outcomes of the specific tumor types may help in predicting behavior. In this study we present the largest series to date on *ROS1* fusion Spitz neoplasms. We present the clinical, morphologic and genomic features of 17 cases. We compared the morphologic features of these 17 cases to a cohort of 99 other non-*ROS1* Spitz neoplasms to assess for features that may have high specificity for *ROS1* fusions. These tumors consisted of 10 Spitz nevi and 7 Spitz tumors. None of the cases met criteria for a diagnosis of Spitz melanoma. Morphologically, the *ROS1* fusion tumors of this series were characterized by a plaque-like or nodular silhouette, often densely cellular intraepidermal melanocyte proliferation, frequent pagetosis, tendency towards spindle cell cytomorphology, low grade nuclear atypia and floating nests with occasional transepidermal elimination. However, there was a significant range in microscopic appearances, including two cases with morphologic features of a desmoplastic Spitz nevus. Different binding partners to *ROS1* were identified with *PWWP2A* and *TPM3* being the most common. No case had a recurrence or metastasis. Our findings document that most *ROS1* fusion Spitz neoplasms have some typical characteristic microscopic features, while a small proportion will have features overlapping with other genomic subtypes of Spitz neoplasms. Preliminary evidence suggests that they tend to be indolent or low grade neoplasms.

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INTRODUCTION

The family of Spitz neoplasms is defined in the most recent edition of the World Health Organization Classification of Skin Tumors (4th edition) as a melanocytic neoplasm with a characteristic Spitz fusion or a mutation in *HRAS* with Spitzoid morphologic features. Recent studies have attempted to correlate specific clinical and morphologic findings in the various fusion subgroups such as *ALK , NTRK1, NTRK3,MAPK, BRAF* and *ROS*1.[1–16] Genomic fusions involving the *ROS1* oncogene are seen in 7 to 17% of Spitz neoplasms.[17, 18] However, thus far only one study of 6 cases has described the morphologic features of *ROS1* Spitz neoplasms.[13]

In this study, we report the clinical, histologic and molecular findings in 17 *ROS1* fusion Spitz neoplasms in order to better characterize this subset of Spitz neoplasms. We compared a number of morphologic features in this set of *ROS1* fusions to a control set of 99 non-*ROS1* Spitz melanocytic neoplasms which have also been assessed by next generation sequencing (NGS). We describe characteristic morphologic features and report those morphologic features statistically more frequent in *ROS1* Spitz compared to other subtypes of Spitz neoplasms. We also report for the first time the occurrence of *ROS1* fusions in two cases of desmoplastic Spitz nevi.

MATERIALS AND METHODS

Case Selection and Genomic Sequencing

Study approval and waiver of consent for use of archived tissue were obtained through the Northwestern Institutional Review Board. The dermatopathology data base at Northwestern was searched for Spitz nevi (SN), atypical Spitz tumor (AST), and Spitz melanomas (SM) in which a ROS1 fusion was identified by NGS. We identified 8 cases matching the above criteria. The paired normal tissue were identified for Case #1, #2, #5 and #6. Additionally nine cases were contributed from the personal consultation files of KJ Busam at Memorial Sloan Kettering Cancer Center in New York. We also identified 99 cases consisting of 20 SN, 53 ST, and 26 SM. Each diagnosis was made at the time of clinical presentation based on morphology with incorporation of FISH or array CGH in select cases. The control group included 59 fusions consisting of the following genes: *ALK* (n = 14), *MAP3K8* (n = 12), *BRAF* (n = 6), *NTRK1* (n = 10), *NTRK3* (n = 6), *RET* (n = 4), *MET* (n = 1), *RASGRF* (n = 1), *RAF1* (n = 1), *MAP3K3* (n = 1), *FGFR* (n = 1), *ERBB4* (n = 1), *PRKDC* (n = 1). Additionally, there were 5 *MAP3K8* truncations. Lastly there were mutations in 19 cases in the following genes: *BRAF* (n = 8), *NRAS* (n = 4), *HRAS* (n = 5), *GNAQ* (n = 1), *ROS1* (n = 1). In 16 cases no known fusions or mutations were identified.

"Spitzoid" morphology was identified according to the World Health Organization Classification of Skin Tumors (4th edition) and other relevant literature. [19–22] NGS with a 1171 cancer related gene panel for DNA and a whole transcriptome sequencing on each case was performed with using the Tempus xO platform and variant-calling. [23, 24] The 1711-gene assay is validated and designed to target therapeutically actionable genes.

Tumor Classification and Clinicopathologic Features

In total there were 17 cases with *ROS1* fusions. The clinical features including age, sex and site of the tumors were summarized from the medical record. Morphologic features were assessed by two board certified dermatopathologist experienced in the assessment of melanocytic tumors. The following morphologic features were evaluated: silhouette (plaque, wedge or nodular), cytology (epithelioid, spindled or both), nuclear atypia (mild, moderate or severe), pigmentation (absent, focal, or extensive), host inflammatory reaction (absent, non-brisk, or brisk), cell size (small, intermediate, large), mitotic figures per mm^2, and for the absence or presence of Kamino body, maturation, ulceration, epidermal hyperplasia, plexiform growth, epithelioid sheets, pagetosis, nesting in the adnexa, and desmoplasia.

Mild nuclear atypia was defined as a slightly larger nucleus than conventional nevomelanocytes. Moderate atypia was defined as a nuclear size similar to the size of keratinocytes with a hyperchromatic nuclear membrane, visible nucleolus, and variable chromatin quality. Severe nuclear atypia was defined as a nuclear size larger than keratinocytes with a hyperchromatic nuclear membrane, prominent and/or multiple nucleoli, and coarse chromatin. For host inflammatory reaction, a brisk response was defined as a diffuse infiltration of lymphocytes across the entire base of the tumor; a non-brisk response was defined as a focal infiltration of lymphocytes that does not cover the entire base.[25] For cell size, the size of melanocytes was compared to the basal keratinocytes.[26] Cells about the size of basal keratinocytes were considered small, those moderately larger than basal keratinocytes were intermediate in size and cells nearly twice the size of basal keratinocytes were considered large. Clinical information including age, gender and site of tumor was also included for analysis.

Statistical Analysis

All statistical analyses were performed in R Studio v1.2.5001 to compare morphologic features across the groups Spitz neoplasms. Fisher's exact test or Chi square test was used to compare associations in categorical variables. Student's t-test was used to compare mean values. A p value of < 0.05 was considered statistically significant. All tests were two-sided.

Data Availability

Data Availability—Processed sequencing data (vcf files and count files) can be found through GEO Series accession number GSE142443 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE142443).

RESULTS

Clinical Findings in *ROS1* Fusion Spitz Neoplasms

The final diagnosis from the time of clinical care in the set of 17 *ROS1* Spitz neoplasms was Spitz nevus in 10 cases and Spitz tumor in 7 cases. In none of the cases was a diagnosis of Spitz melanoma favored. The patient ages ranged from 3 to 58 with a mean age of 19 years old. There were 10 female and 7 male patients. The body site of involvement was highly variable with 4 in the head/neck region, 3 on the upper extremities, 3 on the trunk and 7 on the lower extremities. Grossly, all cases were pink to red papules. In 14 cases the clinical

impression was available. In 7 cases the clinician suspected an atypical Spitz nevus and in one of these cases a dermoscopic description of radial streaming was provided. In 2 cases the clinical impression was dermatofibroma, in 2 cases it was benign nevus, in 2 cases it was pyogenic granuloma and in 1 case it was cyst.

Follow up was available for 13 of 17 cases (Table 1). The average follow up time was 23 months and ranged from 4 months to 95 months. In 12 cases the lesions were re-excised with clear margins with no evidence of recurrence. One of these 12 cases also had a sentinel lymph node biopsy (SLNB) which was negative. In one case the original biopsy was incisional and no further re-excision was performed. There was persistent tumor at a follow exam 4 months later.

Morphologic and Immunohistochemical Findings in *ROS1* Fusions Spitz Neoplasms

The low power silhouette on the 16 *ROS1* cases was mostly that of either a plaque like (n = 7) or nodular pattern (n = 7). Two cases had a wedge shaped silhouette and 1 was polypoid. In 12 cases the cytomorphology was a mixed pattern of epithelioid and spindle cells while in 4 cases there was a predominance of spindle cells. In all cases the atypia was mild or moderate with none of the cases having high grade nuclear atypia (P = 0.006) (Figure 1). This was statistically significant with *ROS*1 cases being less likely to have high grade nuclear atypia than the group of non-*ROS1* Spitz neoplasms. The cell sizes were also all small to intermediate with none of the cases having large cells and this was also statistically significant (P = 0.001). Maturation was present in all cases and this was also statistically significant (P = 0.044). There was also a tendency for lower mitotic rate 1.3/mm^2 (P = 0.001) (Table 2). Kamino bodies were also more common in this type of Spitz (8/17) than non-*ROS1* Spitz (P = 0.025).

Thirteen of 17 cases had overlying epidermal hyperplasia. Fourteen of 17 cases were completely amelanotic. Lobulated nests were seen in 2 cases and nesting in the adnexa in 5 cases. Five cases had notable pagetosis in the epidermis. None of these features were statistically significant compared to non-*ROS1* Spitz neoplasms. Nine of 17 cases had floating nests defined as nests situated above the basal layer and in 3 cases there was transepidermal elimination of nests (Figure 1 and 2). Myxoid changes were not identified in any of the cases. Two cases were characterized by prominent stromal desmoplasia, and were morphologically best characterized as a desmoplastic Spitz nevus (Figure 3).

Immunohistochemical Staining for *ROS1* was performed in 16 cases. Fifteen of the 16 cases showed strong positive staining (Figure 4). In one case only a blush staining was seen which was not convincingly positive.

Genomic Findings in *ROS1* Fusion Spitz Neoplasms

The fusion partner was identified in 16 of the 17 cases in the study. The most common genomic fusions among the 16 *ROS1* cases were a *PWWP2A-ROS1* fusion seen in 6 cases and a *TPM3-ROS1* fusion also seen in 5 cases. Other recurrent fusion partners included a *PPFIBP1-ROS1* fusion seen in 2 cases, and fusions partners involving *MYH9-ROS1*, *CAPRINI1-ROS1* and *MYO5A-ROS1* were each seen in 1 case (Table 3).

Three cases had copy number aberrations identified by NGS and SNP arrays. Two cases had copy number aberrations identified by NGS and 1 case had a copy number aberration identified by SNP array. Copy number loss of *BCL11B*, *FGF3*, *CARD11*, *FBXO11*, *FLT4*, *GRIN2A*, *HGF*, *MGMT*, *MYCN*, *MYOD1*, *NPM1*, *NTRK3*, *PLAG1*, *PTPRT*, *RET*, *TERT* and *TLX1* were identified in case 2. This case was negative for copy number alterations when tested by a SNP array platform. Copy number gains of *HOXA9*, *JUN*, *MDM2* were identified in case 6. Case 10 had an isolated loss at 6q.

DISCUSSION

Among two studies sequencing a large number of Spitz neoplasms the frequency of *ROS1* fusions varied from 7 to 17%.[17, 18] The vast majority of these cases were diagnosed as either Spitz nevus or Spitz tumor. In this study 10 were diagnosed as Spitz nevus and 7 as Spitz tumor. We did not identify any cases that met the criteria of a Spitz melanoma. In the study from Wiesner et al where kinase fusions in Spitz neoplasms were first described,[17] 3 of 24 *ROS1* fusions were designated as Spitz melanoma, but no adverse clinical outcome was reported. This study from Wiesner et al is the larger series on ROS1 fusions but does not discuss morphologic features. Thus far there is only one study involving 6 cases of ROS1 fusions which were all designated as Spitz tumors by Donati et al which discusses morphologic features.[13]

While there is limited clinical outcomes information available on Spitz tumors with *ROS1* fusions, among the 13 cases with follow up in this study and the 6 cases from Donati et al, there are no reported recurrences or metastases after complete excision of the primary tumors. One case in our series had a SLNB which was also negative. Thus, preliminary evidence suggests that most Spitz tumors with *ROS1* fusions are likely indolent or at least in a much lower risk category compared to Spitz neoplasms with *BRAF* or *MAP3K8* fusions which seem to constitute much of the more aggressive variants of Spitz neoplasms.[9–11, 15, 27–29]

We did not identify morphologic features which could allow for a definitive diagnosis of a *ROS1* fusion by microscopic review alone but there were some characteristic features. This included a tendency for plaque-like or nodular silhouette without a deeply infiltrative component with a combination of epithelioid and spindle cell cytomorphology. Statistically significant features included lack of high grade cytologic atypia in all cases, lack of larger cell type, presence of maturation, frequent Kamino bodies and lower mitotic rate. These findings are consistent with the fact that all cases were diagnosed as Spitz nevus or Spitz tumor and none were thought to be Spitz melanoma.

In our cases, 13/17 had epidermal hyperplasia and 5/17 had notable epidermal pagetosis. Two cases had lobulated nests and 4 had nesting in the adnexa. None of these features were statistically significant as they can be seen in a broad spectrum of Spitz subtypes. In particular many of these features can overlap with *NTRK1* fusion Spitz neoplasms. Donati et al reported transepidermal elimination of nests and myxoid changes as being present in all 6 cases. Another highly characteristic feature was floating nests seen in 9 of 17 cases with transepidermal elimination of nests in 3 cases. We did not identify significant mucinous

changes though a colloidal iron was not performed. Although none of these features are totally specific, one might anticipate a ROS1 fusion in compound plaque like Spitz neoplasm with prominent intraepidermal component, Kamino bodies, with small to intermediate sized cells with low grade cytology, pagetosis and floating nests within the epidermis.

An interesting and novel observation is the detection of a *ROS1* fusion in two desmoplastic Spitz nevi. This illustrates the wide spectrum of microscopic features associated with *ROS1* fusions, but it also documents that the desmoplastic phenotype among Spitz nevi is not limited to *HRAS* aberrations. Gains of 11p (location of *HRAS*) and/or *HRAS* mutations have previously been thought to be typical of desmoplastic Spitz nevi. While they likely represent the most common aberration associated with a desmoplastic Spitz nevus, we hereby document two cases with a ROS1 kinase fusion associated with a desmoplastic phenotype.

In the 17 cases in this series, 6 different fusion partners were identified. This included *PWWP2A* (n = 6), *TPM3* (n = 5), *PPFIBP1* (n = 2), *MYO5A* (n = 1), *CAPRINI1* (n = 1) and *MYH9* (n = 1). *PWWP2A* was also the most frequent fusion partner in the series from Donati et al. A figure showing the chimeric protein model and the breakpoint of the fusions can be found in Figure 5. Previous *in vivo* studies show rising levels of phosphorylation produced by this fusion protein indicating that the *ROS1* kinase is being constitutively activated.[17]

ROS1 fusions have been identified in 9% Spitz melanomas and 1.3% in melanomas from previous studies.[17, 30] There are no cases of *ROS1* fusion melanoma in the TCGA database. *ROS1* fusions are also seen in a subset of 1 to 2 % non small cell lung cancers. More recently *ROS1* fusions were identified in 9 of 130 gliomas from an infant population.[31] Also, rare cases of *ROS1* fusions in angiosarcoma, thyroid and breast cancer have been reported.[32–34] Interestingly in melanocytic neoplasms with *ROS1* fusions the tumors seem to have an indolent clinical behavior.

In conclusion, this study describes the largest series to date on *ROS1* fusion Spitz neoplasms. They seem to represent a lower grade group of tumors with generally indolent behavior. We could not find specific morphologic aberrations that were predictive of the molecular aberration but identified a number of features that were enriched in the group of *ROS1* fusion tumors. They included a plaque or nodular silhouette with a cellular intraepidermal component, frequent Kamino bodies, a slight predisposition towards spindle cytology, a lower grade of cytologic atypia and floating nests/transepidermal elimination of nests. We also report for the first time the association of a desmoplastic phenotype with *ROS1* fusions.

Acknowledgments

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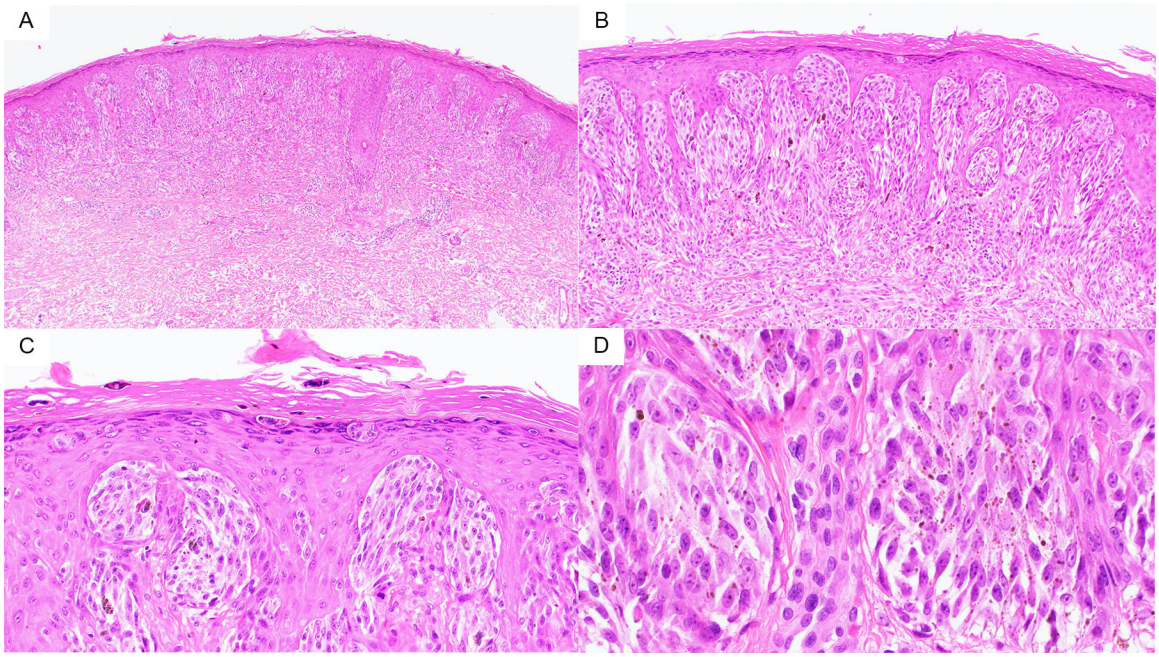

Figure 1).

A) At 40X one can appreciate the plaque like silhouette of this *ROS1* Fusion Spitz Neuvs B) At 100X the epidermal hyperplasia with a predominance of nests with spindle shaped melanocytes can be seen C) At 200X one can appreciate the transepidermal elimination of small nests into the stratum corneum. D) 400X demonstrates the Spitzoid cytomorphology with relatively low grade nuclear atypia.

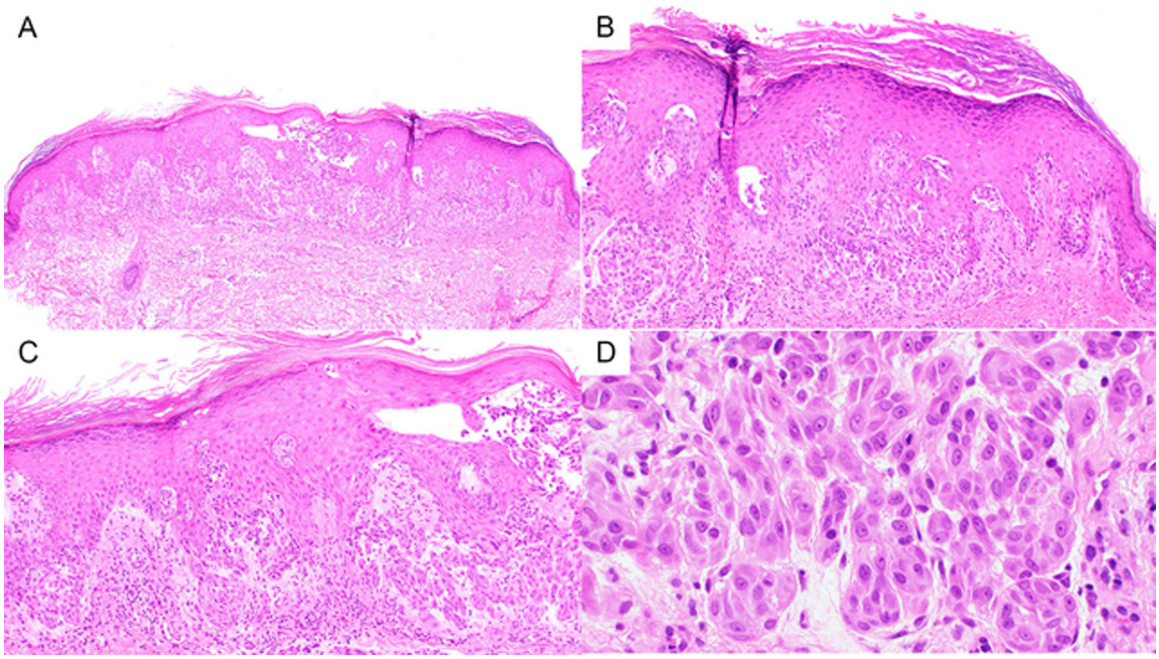

Figure 2).

A and B) At 40x and 100X, respectively, a plaque like Spitz nevus with epidermal hyperplasia. C) At 200X one can appreciate some floating nests in the epidermis D) At 400X one can appreciate the relatively bland cytology of the Spitzoid melanocytes.

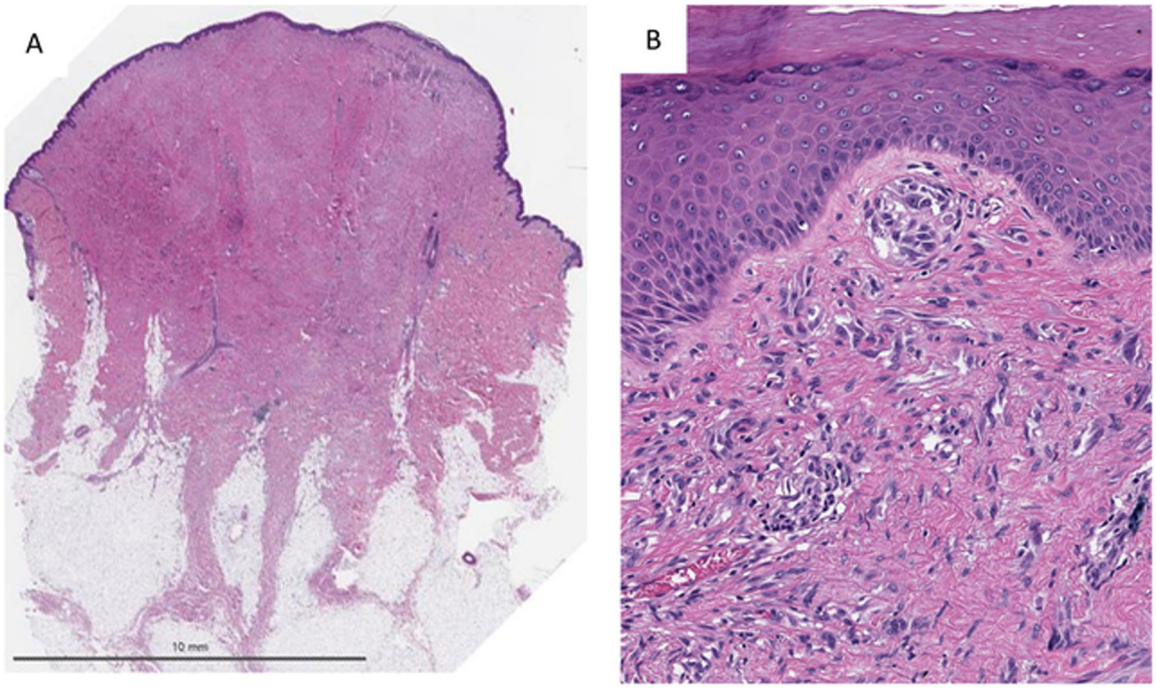

Figure 3).

A) Low power shows a symmetric paucicellular Spitzoid neoplasm in a desmoplastic Stroma. B) Higher magnification shows small nests and individual units of Spitzoid melanocytes entrapped in a sclerotic stroma consistent with a diagnosis of desmoplastic Spitz nevus.

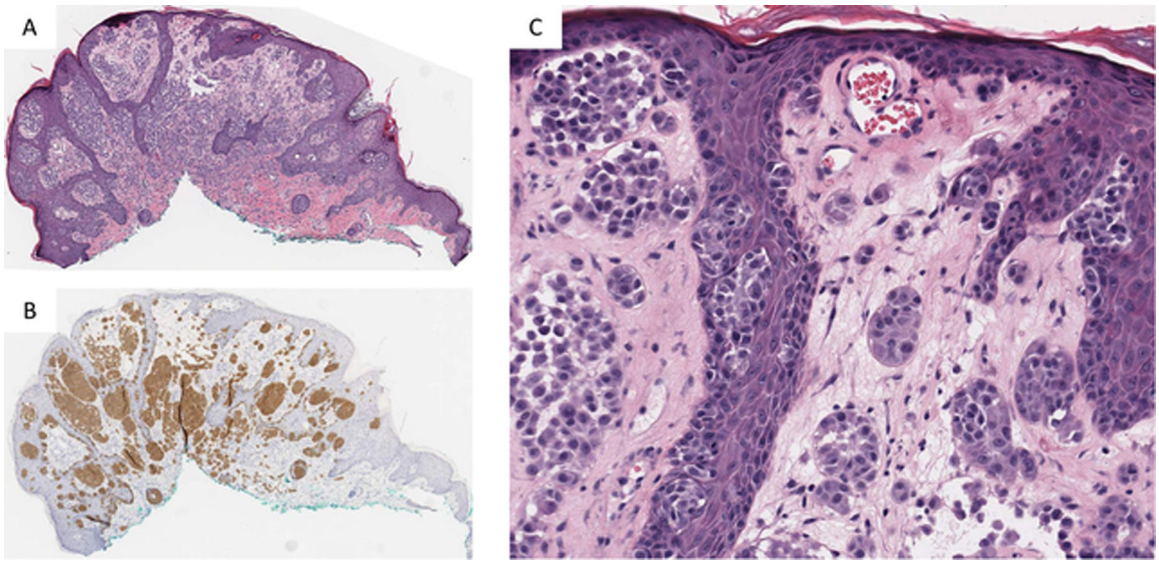

Figure 4).

A) Low power showing plaque like silhouette of a *ROS1* Fusion Spitz nevus. B) IHC staining for ROS1 shows strong and uniform staining throughout the nevus. C) Higher magnification shows nests of epithelioid and spindle shaped melanocytes with bland cytomorphology lacking significant atypia.

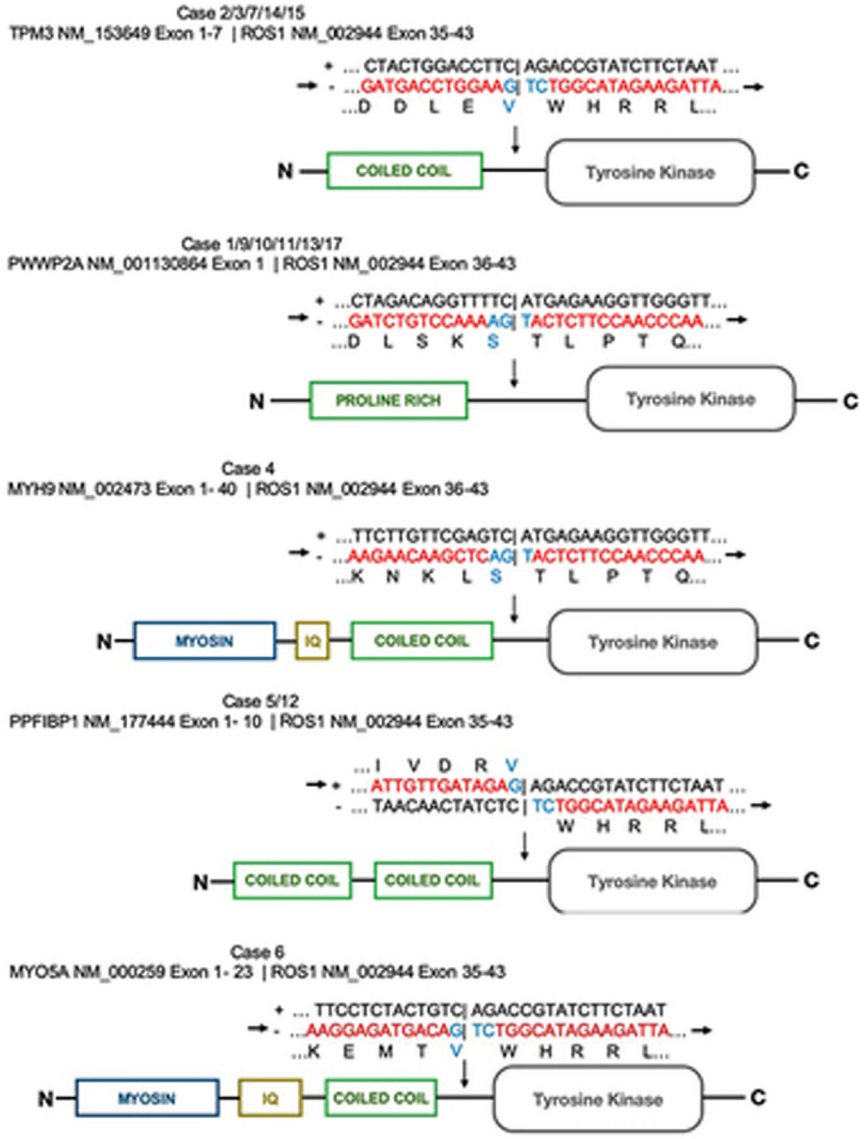

Figure 5).

Diagrams of the chimeric fusion proteins in the *ROS1* fusion Spitz neoplasms

Table 1.

Summary of clinical data in 16 cases of Spitz neoplasms with *ROS1* fusions

Case	Age	Gender	Location	Diagnosis	Clinical impression	Surgical Treatment	SLNB	Metastasis	Follow up	Recurrence
1	34	F	Right lower medial leg	Atypical Spitz tumor	Rule out atypical nevus vs Spitz nevus vs malignant melanoma; 6 x 4 mm color variated pink brown papule with radial streaming pattern at edges	Complete excision	No	No	24 months	No
2	37	F	Left anterior medial thigh	Atypical Spitz tumor	5.5 mm erythematous papule; dermatofibroma – check margins	Complete excision	No	No	95 months	No
3	28	F	Left thigh	Atypical Spitz tumor	Cyst	Complete excision	No	No	64 months	No
4	13	F	Left upper arm	Spitz nevus	Re-excision; rule out Spitz nevus	Complete excision	Not available	Not available	Not available	Not available
5	20	F	Left buttock	Spitz nevus	Intradermal nevus, rule out atypa	None	No	No	Not available	Not available
6	6	M	Right buttock	Spitz nevus	Changing nevus, rule out Spitz nevus	Complete excision	No	No	35 months	No
7	36	F	Left shin	Atypical Spitz tumor	Melanocytic lesion, rule out atypical Spitz tumor	Not available	Not available	Not available	Not available	Not available
8	12	F	Right ear	Atypical Spitz tumor	None provided	Incisional biopsy without further re-excision	No	No	4 months	Persistent tumor 4 months later
9	15	M	Left neck	Spitz nevus	Rule out Spitz nevus	Complete excision	No	No	15 months	No
10	15	M	Right upper arm	Atypical Spitz tumor	Pyogenic granuloma versus hypertrophic scar	Complete excision	No	No	11 months	No
11	9	M	Right ear	Spitz nevus	Nevus, rule out atypia	Complete excision	No	No	10 months	No
12	18	M	Left mid back	Spitz nevus	Spitz nevus	Complete excision	No	No	9 months	No
13	17	M	Left upper back	Desmoplastic Spitz nevus	Dermatofibroma	Complete excision	No	No	5 months	No
14	3	M	Left ear	Spitz nevus	Rule out pyogenic granuloma	Complete excision	No	No	13 months	No
15	4	F	Left knee	Spitz nevus	Rule out Spitz nevus	Complete excision	No	No	13 months	No
16	58	F	Left arm	Atypical Spitz tumor	None provided	Complete excision	Yes, negative	No	6 months	No

Case	Age	Gender	Location	Diagnosis	Clinical impression	Surgical Treatment	SLNB	Metastasis	Follow up	Recurrence
17	6	F	Abdomen	Desmoplastic Spitz nevus	None provided	Complete excision	No	No	Not available	No

SLNB, sentinel lymph node biopsy; F, female; M, male;

Table 2.

Comparison of Clinical and Morphologic Findings in *ROS1* and non-*ROS1* fusion Spitz neoplasms

	All (n = 116)	Non-*ROS1* vs *ROS1*		
		Non-*ROS1* (n = 99)	*ROS1* (n = 17)	P
Clinical				
Age, years				0.75
Mean	20.5	20.7	19.5	
Range	1–65	1–65	3–58	
Gender				0.80
Female	64	54	10	
Male	52	45	7	
Location				0.68
Head/Neck	23	19	4	
Upper Extremity	33	30	3	
Trunk	15	12	3	
Lower Extremity	45	38	7	
Histologic				
Tumor Subtype				0.003
SN	29	20	9	
AST	61	53	8	
SM	26	26	0	
Tumor depth, mm				0.32
Mean	2.04	1.88	2.93	
Range	0.25–17.0	0.25–12.2	0.40–17.0	
Tumor Diameter, mm				0.71
Mean	4.78	4.74	5.02	
Range	0.69–16.5	0.69–16.50	2.90–14.0	

Mod Pathol. Author manuscript; available in PMC 2021 February 28.

	All (n = 116)	Non-*ROS1* vs *ROS1*		
		Non-*ROS1* (n = 99)	*ROS1* (n = 17)	P
Silhouette				0.16
Plaque	49	42	7	
Wedge	31	29	2	
Nodular	34	27	7	
Polypoid	2	1	1	
Cytology				0.17
Epithelioid	25	24	1	
Spindled	30	26	4	
Both	61	49	12	
Nuclear Atypia				0.006
Mild	11	10	1	
Moderate	74	58	16	
Severe	31	31	0	
Kamino body				0.025
Absent	89	80	9	
Present	27	19	8	
Pigmentation				0.10
Absent	66	52	14	
Focal	29	27	2	
Extensive	21	20	1	
Maturation				0.044
Absent	18	18	0	
Partial	26	19	7	
Present	72	62	10	
Ulceration				0.62
Absent	107	92	15	

	All (n = 116)	Non-*ROS1* vs *ROS1*		
		Non-*ROS1* (n = 99)	*ROS1* (n = 17)	P
Present	9	7	2	
Inflammatory Reaction				0.04
Absent	7	4	3	
Non-Brisk	68	57	11	
Brisk	41	38	3	
Epidermal Hyperplasia				0.49
Absent	20	16	4	
Present	96	83	13	
Plexiform				0.42
Absent	73	64	9	
Present	43	35	8	
Epithelioid Sheet				0.04
Absent	94	77	17	
Present	22	22	0	
Pagetosis				0.32
Absent	93	81	12	
Present	23	18	5	
Cell Size				0.001
Small	21	20	1	
Intermediate	65	49	16	
Large	30	30	0	
Nesting Adnexa				0.15
Absent	97	85	12	
Present	19	14	5	
Lobulated Nests				0.73

	All (n = 116)	Non-*ROS1* vs *ROS1*		
		Non-*ROS1* (n = 99)	*ROS1* (n = 17)	P
Absent	95	80	15	
Present	21	19	2	
Mitotic index (per mm²)				0.001
Mean	2.2	2.34	1.30	
Range	0–20	0–20	0–4	

Table 3.

Genomic Fusions in *ROS1* Spitz Neoplasms

Case	Fusion	Copy Number Variation
1	*PWWP2A-ROS1*	None identified
2	*TPM3-ROS1*	Copy loss: *BCL11B, CARD11, FBXO11, FGF3, FLT4, GRIN2A, HGF, MGMT, MYCN, MYOD1, NPM1, NTRK3, PLAG1, PTPRT, RET, TERT, TLX1*
3	*TPM3-ROS1*	None identified
4	*MYH9-ROS1*	None identified
5	*PPFIBP1-ROS1*	None identified
6	*MYO5A-ROS1*	Copy gain: *HOXA9, JUN, MDM2*
7	*TPM3-ROS1*	None identified
8	Identified by FISH Breakapart Probe	None identified
9	*PWWP2A-ROS1*	None identified
10	*PWWP2A-ROS1*	Copy loss: 6q.22.1 *
11	*PWWP2A-ROS1*	None identified
12	*PPFIBP1-ROS1*	None identified
13	*PWWP2A-ROS1*	None identified
14	*TPM3-ROS1*	None identified
15	*TPM3-ROS1*	None identified
16	*CAPRIN1-ROS1*	Not assessed
17	*PWWP2A-ROS1*	None identified

* Identified by SNP array