Filigree-like Rete Ridges, Lobulated Nests, Rosette-like Structures, and Exaggerated Maturation Characterize Spitz Tumors With NTRK1 Fusion

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01 背景知识

BACKGROUND

背景知识
BACKGROUND

Spitz痣

ICD-O代码 8770/0

临床表现：常见于20岁以内；发病率随年龄增长而下降，与皮肤黑色素瘤相反； 部位：下肢，面部（儿童）和躯干（成人）。直径在1mm左右，最大者可超过2cm。粉色或红色丘疹，边界为类圆形，中央呈球形隆起；几乎不形成溃疡

组织病理学：<6mm；对称；病变较局限；表皮增生；表皮内痣细胞巢与表皮突方向一致，黑色素细胞在细胞巢内垂直生长，细胞巢周裂隙明显。痣细胞为梭形细胞、上皮样细胞或两者均有

可以是交界痣、复合痣或皮内痣

背景知识
BACKGROUND

Spitz痣

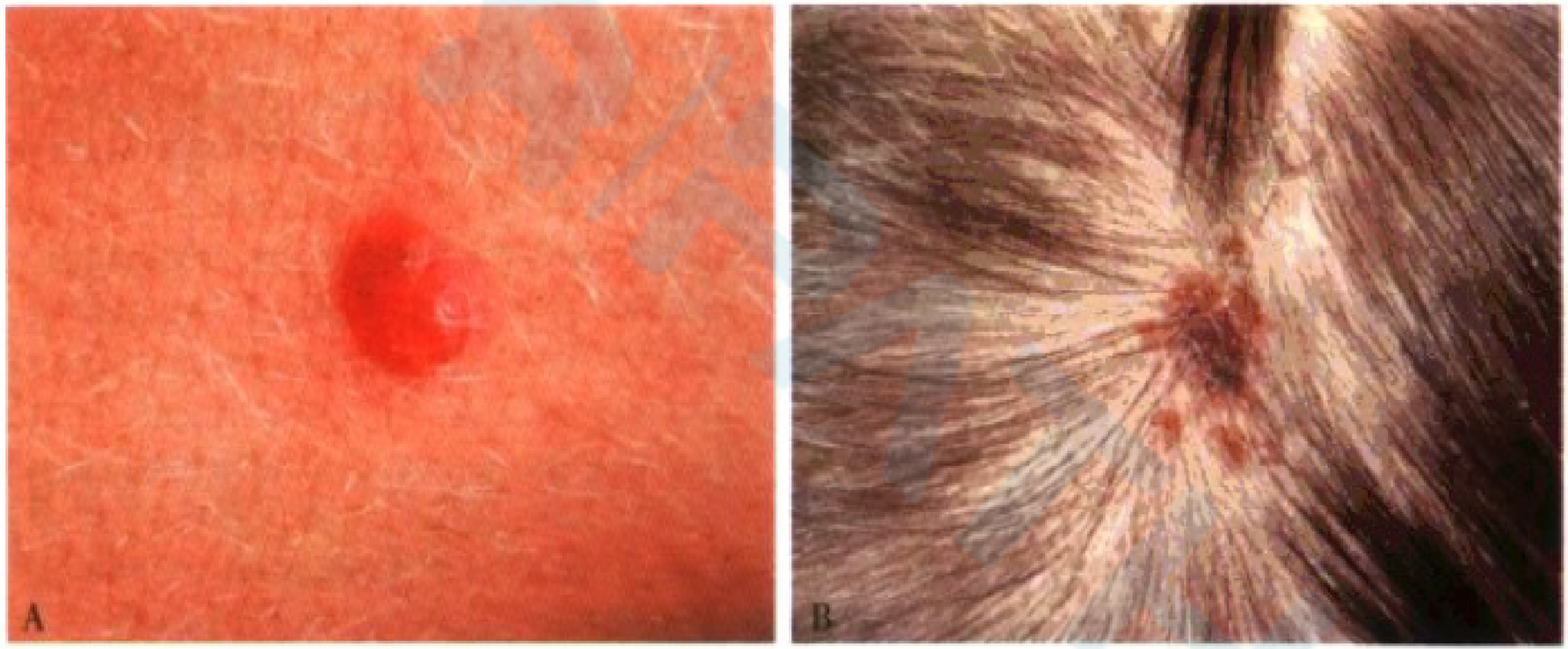
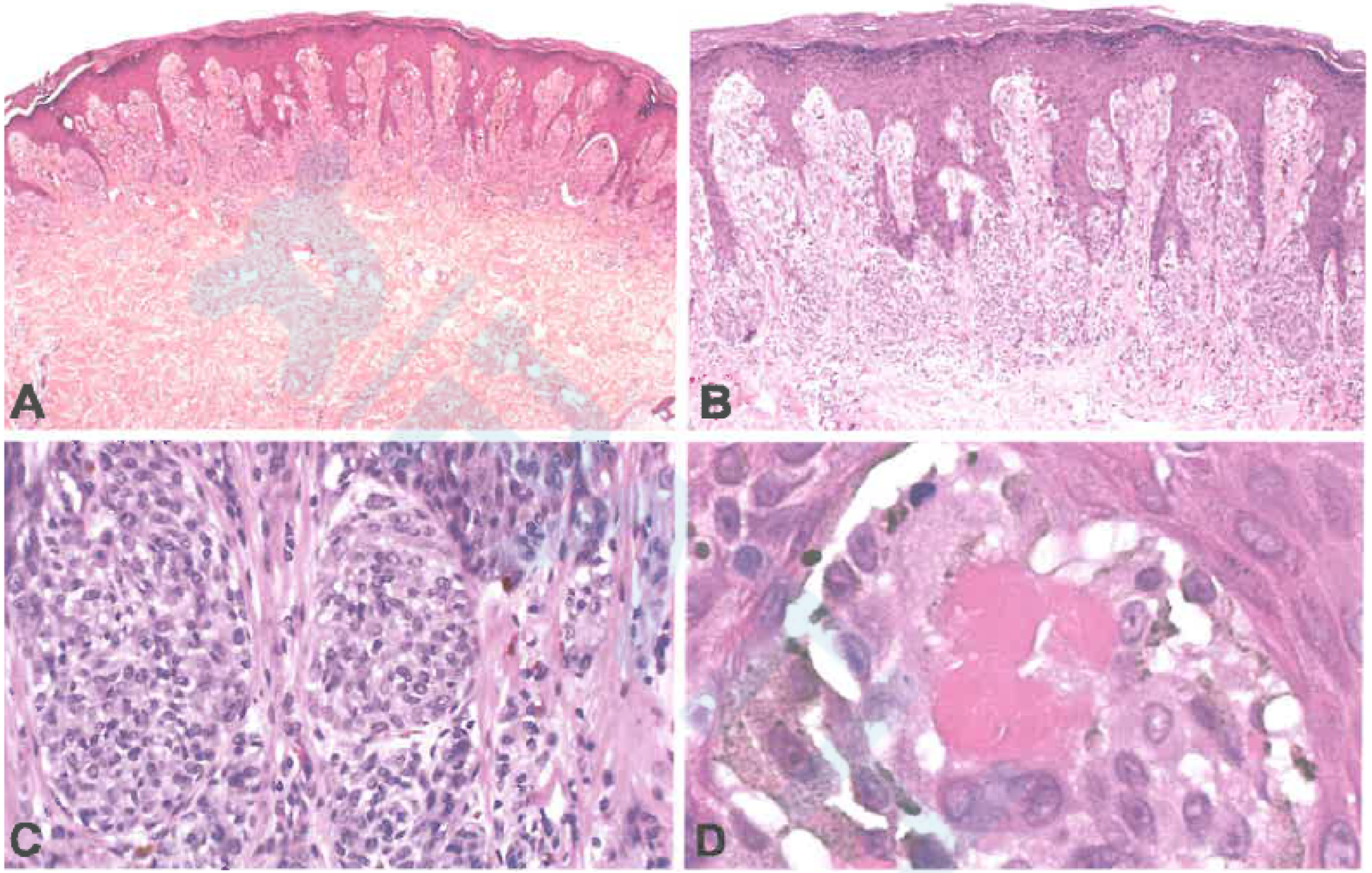


图 2.66 Spitz 痣。**A.** 境界清楚的半球形病变，可能被误认为血管瘤。**B.** 病变由小的棕色丘疹聚集形成，这种结构常会引起警惕。

参考WHO皮肤肿瘤病理学和遗传学

背景知识
BACKGROUND

Spitz痣



Spitz痣。A病变直径4.2毫米，厚度0.9毫米。有对称性，均匀的表皮增生和黑素细胞垂直排列。B在真皮表皮交界处有垂直的黑色素细胞束。表皮增生，黑素细胞成熟后延伸到真皮中;无核分裂。C增大的梭形细胞和上皮样细胞具有嗜酸性胞质;无异型性。D嗜酸性均质小体（Kamino体）被上皮样细胞和梭形黑素细胞包围。5年的随访中没有复发。

参考WHO Classification of Skin Tumour（2018）

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Spitz痣

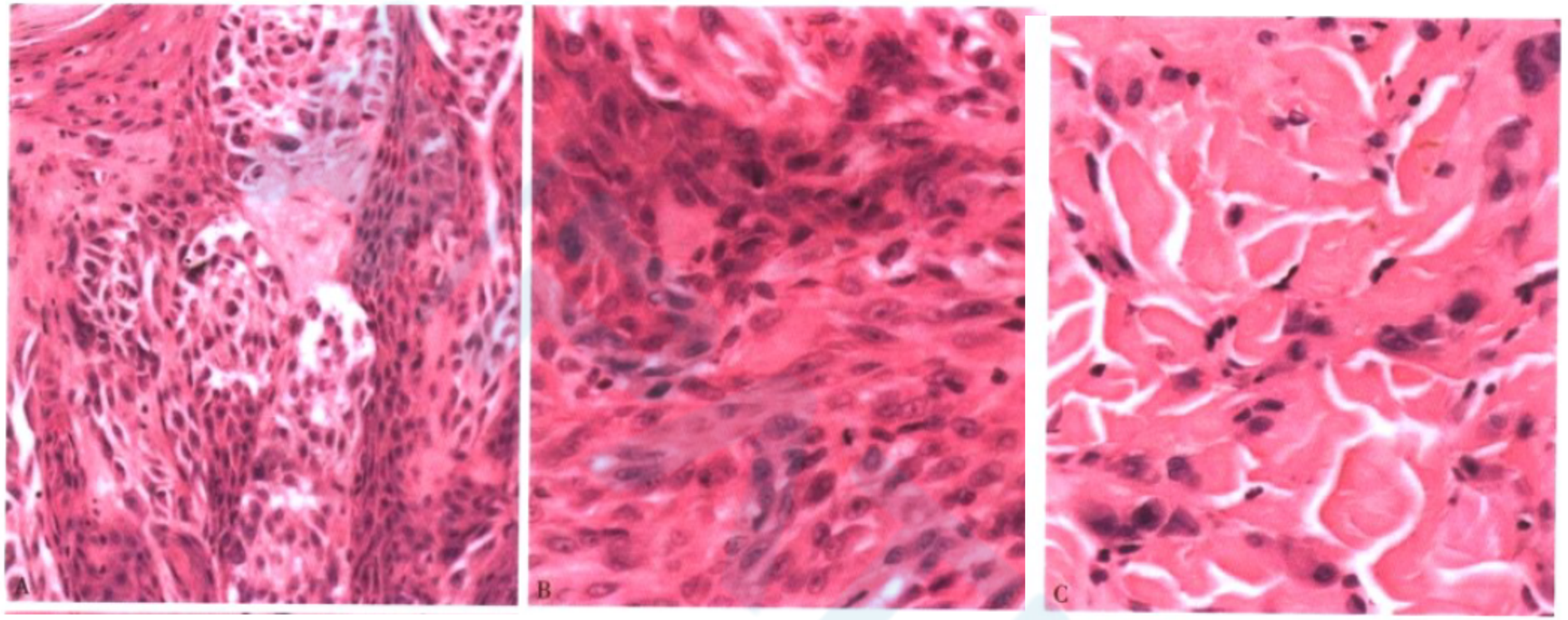

图2 Spitz痣，混合性。A. Spitz痣的交界性成分，伴表皮增生。2.病变上部细胞丰富。3.病变基底部可见单个大的卵圆形黑色素细胞穿插于宽的胶原纤维束之间。

参考WHO皮肤肿瘤病理学和遗传学

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不典型Spitz肿瘤（AST）

临床表现： 可发生于任何年龄; 常见于年轻患者(<40岁);
发生在躯干;
斑块或多种颜色结节;
很少转移

组织病理学：>5-10mm；对称或不对称；可伴有溃疡;
派杰样播散比Spitz痣范围广，延伸深;
可见核分裂（2-6个）;
较Spitz痣核增大，核多形性，高核浆比，
可见大嗜酸性核仁

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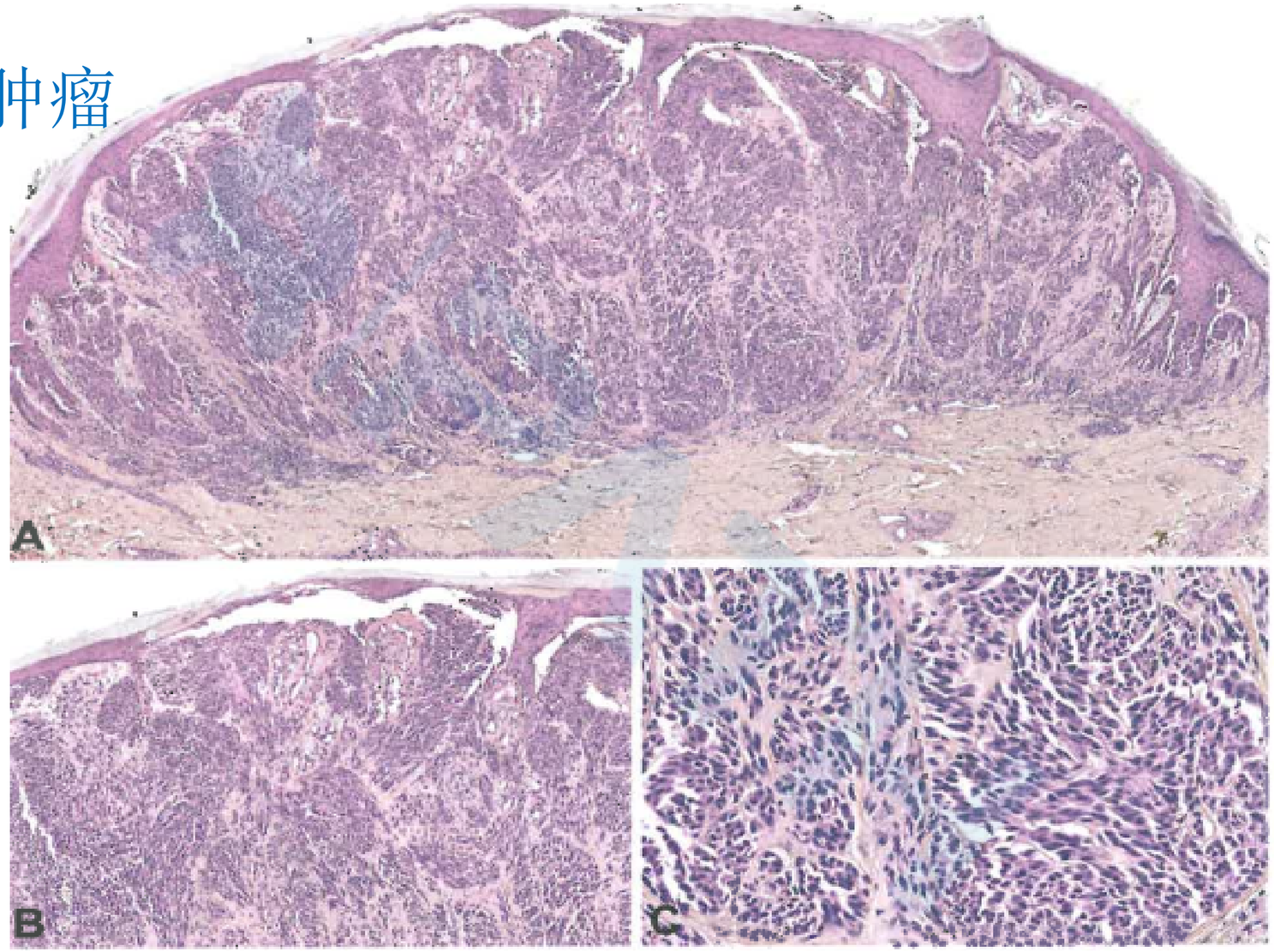
不典型Spitz肿瘤



不典型Spitz肿瘤。对称，边界清楚，高倍镜显示表皮的萎缩，梭形黑素细胞排列密集。肿瘤底部有密集的非典型黑素细胞巢。可见核分裂像。

参考WHO Classification of Skin Tumour（2018）

背景知识
BACKGROUND

恶性Spitz肿瘤（MST）

ICD-O代码 8770/3

临床表现：常＞40岁，四肢，躯干不对称扩大的斑块或结节

组织病理学：>5mm，经常>10mm；不对称；界限不清；浸润皮下脂肪；
有溃疡；派杰样播散范围广，延伸深；
核分裂（＞6个）及坏死多见；成熟现象减少或消失;
血管生成;淋巴血管侵犯;明显的细胞学异型性
核增大，多形性，核膜增厚和不规则，核浆比增加，
染色质聚集，嗜酸性核仁增大

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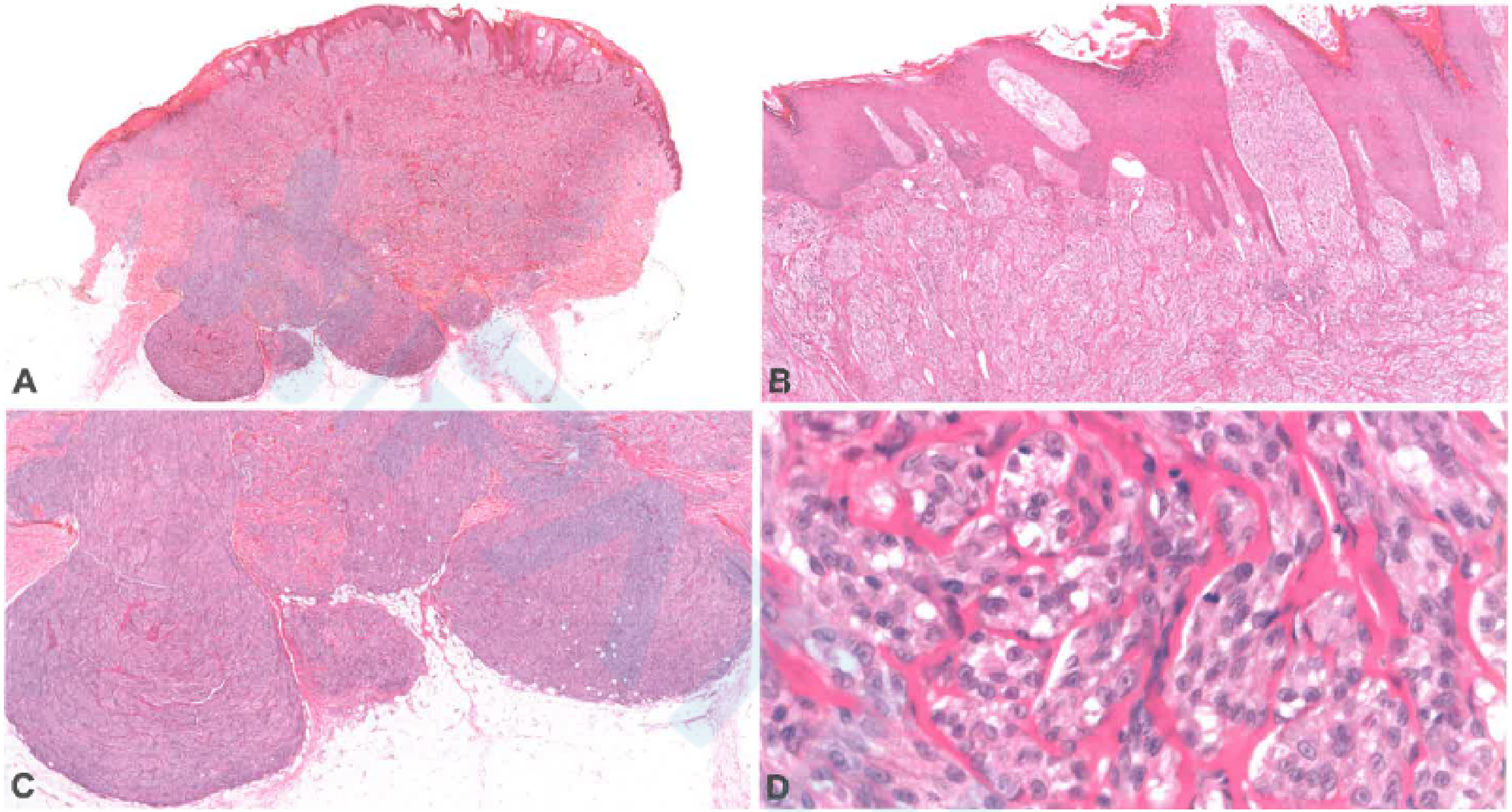
恶性Spitz肿瘤



恶性Spitz肿瘤。图A:11岁、女、大腿上有一不对称和溃疡的肿瘤延伸到皮下脂肪中。肿瘤直径12毫米，厚7毫米;没有观察到成熟现象。B表皮增生和垂直生长的黑素细胞巢。C肿瘤延伸到皮下脂肪而且不成熟;细胞密集。D高倍镜下梭形细胞束状排列;7 个核分裂 / mm2;并且有TERT突变。该患者诊断后6个月时局部淋巴结转移并在24个月时死于广泛转移。

参考WHO Classification of Skin Tumour（2018）

背景知识 Spitz痣、不典型Spitz肿瘤和恶性Spitz肿瘤鉴别诊断

BACKGROUND

	Spitz痣	不典型Spitz肿瘤	恶性Spitz肿瘤
免疫组化	HMB-45和Ki-67染色随病变深度递减，Ki-67增殖指数低(< 5%)。	HMB45和Ki-67染色随病变深度递减或变化，Ki-67增殖指数（5-15%）	HMB45和Ki-67通常深染，Ki-67增殖指数(>20%)，p16表达减少或缺失
分子病理学	aCGH：7p和11q的孤立性增益，四倍体 HRAS突变 激酶融合	aCGH：常≥1染色体异常 PTEN突变 可能出现9p21杂合子或纯合子的丢失	aCGH：> 1染色体异常 PTEN及TERT启动子突变 BRAF、NRAS、HRAS突变罕见 9p21 纯合子丢失
预后	低或无风险	低风险，几乎总是惰性	可发生区域淋巴转移 罕见远处转移和死亡

参考WHO Classification of Skin Tumour（2018）

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大多数Spitz nevi含有HRAS突变（22%），ROS1（19%），ALK（8%）的基因融合，NTRK1（8%），BRAF（4%），RET（2%），MET（1%），NTRK3（1%）

与普通痣和先天性痣相比，Spitz痣具有多种起始癌基因，Spitz痣中存在的致癌基因具有不同的致癌信号输出，这可能引发组织病理学和临床表型的差异

Spitz痣可能存在多种亚型，这种复杂性可能会增加普通显微镜诊断的难度

背景知识

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American Journal of Pathology, Vol. 157, No. 3, September 2000

Mutations and Copy Number Increase of *HRAS* in Spitz Nevi with Distinctive Histopathological Features

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debate whether Spitz nevus and melanoma reside at the opposing ends of a biological spectrum[3] or represent two separate entities.[4] The diagnostic uncertainty of cases with overlapping histological criteria is expressed in terms like atypical Spitz nevus, malignant Spitz nevus, and spitzoid melanoma. The lack of diagnostic selectivity

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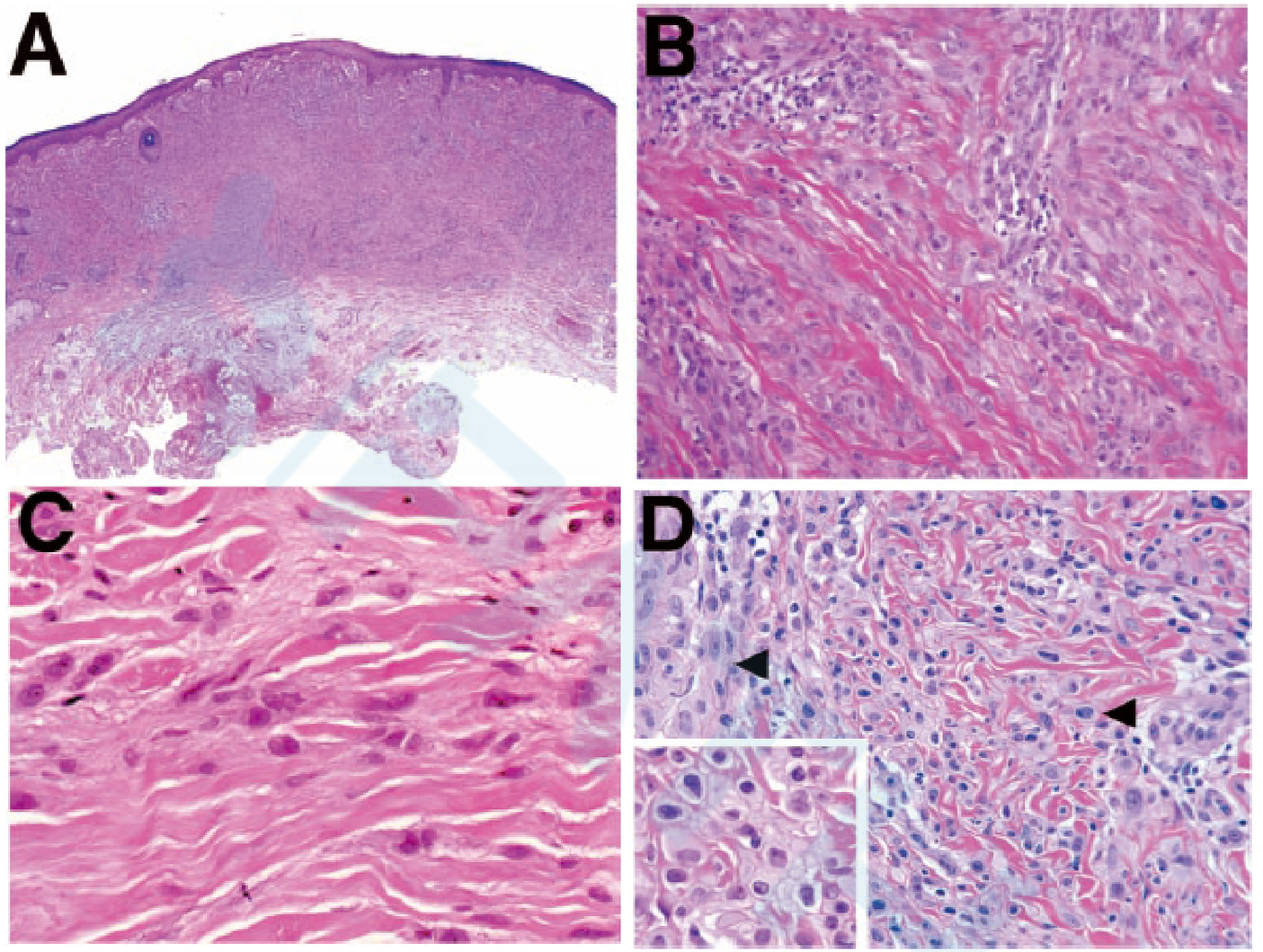

与11p拷贝数增加相关的组织学特征（HRAS基因位于染色体11p的顶端）。A：混合痣，主要是皮内Spitz痣。B：丰富的双嗜性胞浆和水泡状核的黑素细胞，在胶原纤维之间穿插排列且核仁明显。C：具有多形核的黑素细胞单独排列在增厚的胶原纤维之间。d :细胞被嗜酸性物质包围。

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Clinical, Histopathologic and Genomic Features of Spitz Tumors with ALK Fusions

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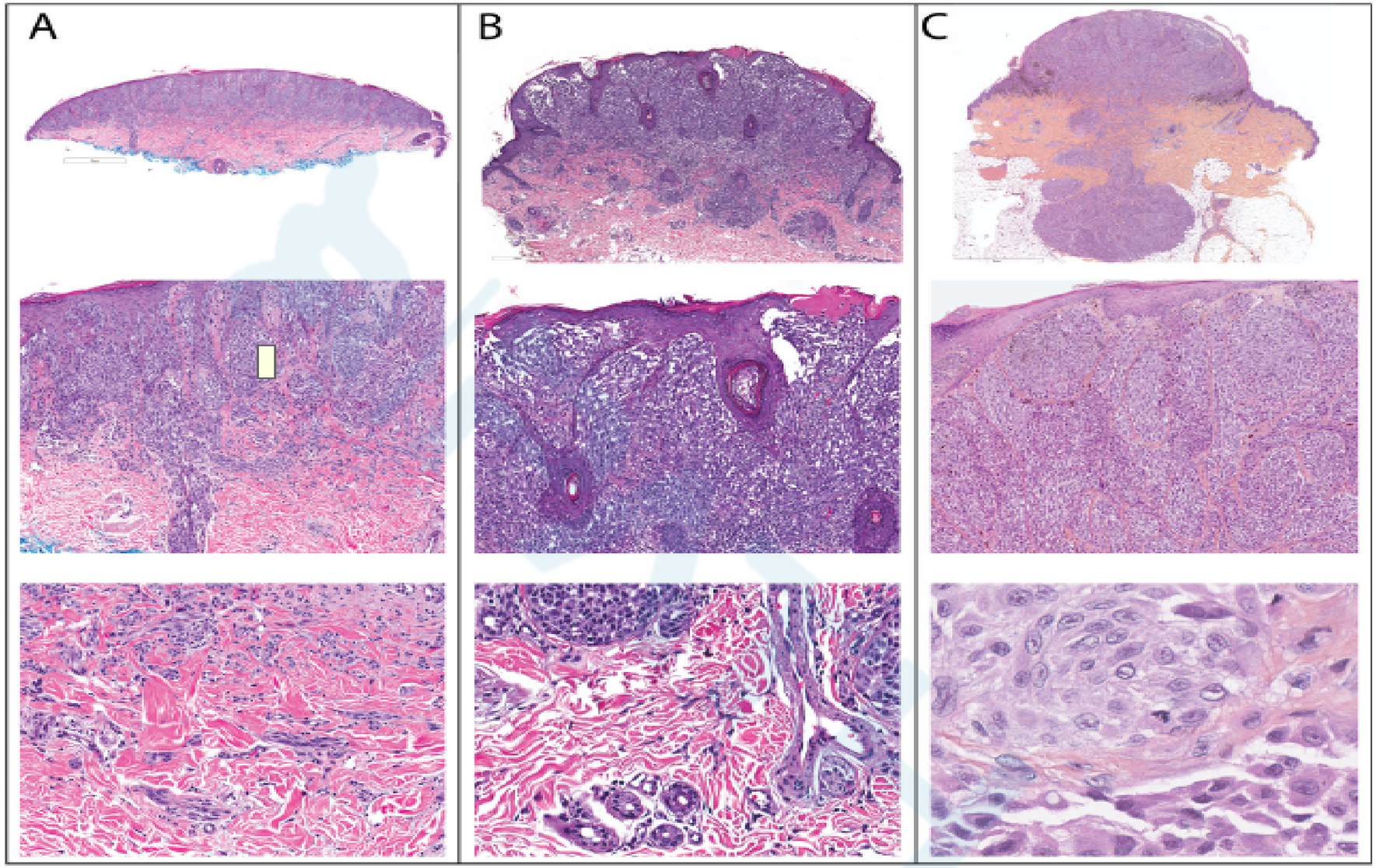

ALK融合Spitz肿瘤的结构特征

A.外生型肿瘤，底部平坦。被覆上皮增生，肿瘤细胞垂直方向束状排列。黑素细胞沿外分泌导管延伸。在基部，黑素细胞穿插胶原束之间。B.具有楔形基部的外生性肿瘤。存在细长的网状脊，在黑素细胞束上方有可见灶性溃疡。单个黑素细胞存在于基部的胶原束之间。C.“哑铃”构型的外生性肿瘤，球状基部延伸到皮下组织。在乳头状真皮中存在大的梭形黑素细胞束。在肿瘤的深部可见核分裂

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HRAS突变的Spitz nevi

病变主要在真皮，具有平坦的轮廓，丰富的双嗜性胞浆和泡状核的黑素细胞，在胶原纤维之间穿插排列且核仁明显

ALK融合的Spitz肿瘤

通常是外生的，梭形的黑素细胞增殖穿插胶原束之间，楔形基部或球状基部浸润到皮下组织

研究目的

RESEARCH OBJECTIVES

在本次研究中，回顾了包含NTRK1融合的38个Spitz肿瘤，并进一步确定了它们的临床，组织病理学和基因组特征。

02 材料和方法

MATERIALS AND METHODS

材料和方法
MATERIALS AND METHODS

从3个医疗中心收集具有NTRK1融合的黑素细胞肿瘤

免疫组织化学：TrkA（ab7929)

荧光原位杂交（FISH）

阵列比较基因组杂交（Array Comparative Genomic Hybridization,aCGH)

（1774 diagnostically challenging melanocytic tumors）

DNA或RNA测序

材料和方法
MATERIALS AND METHODS

组织病理学分析：

I.Y., A.d.l.F., B.C.B., T.H.M., P.E.L., K.J.B.

03 结果

RESULTS

结果
RESULTS

Spitz痣
8例
21%

不典型
Spitz肿瘤
26例
68%

TABLE 1. Clinical Features of Spitz Tumors With *NTRK1* Fusion

Case	Age (y)	Sex	Site	Clinical Description	Final Diagnosis	Breslow Depth (mm)	Clinical Follow-up (Time)	Fusion Partner	Copy Number Aberrations
1	2	M	Cheek	5×6 mm pink papule, Spitz nevus or juvenile xanthogranuloma	Spitz nevus	2.9	No recurrence (4 y)	*LMNA*	Deletion between *LMNA* and *NTRK1*
2	8	F	Face	Recent change	Spitz nevus	2	No recurrence (3 mo)	NA	NA
3	14	M	Back	Raised pedunculated irritated nevus; onset 3 mo ago, also has lesions on lower abdomen, purplish, possible hemangioma	Spitz nevus	3.4	NA	*LMNA*	Deletion between *LMNA* and *NTRK1*
4	14	M	Shoulder	Atypical	Spitz nevus	2	No recurrence (2 y)	NA	NA
5	22	F	Back	Enlarging lesion×3 mo, small, well circumscribed, symmetrical	Spitz nevus	1.4	No recurrence (6 y)	*LMNA*	Deletion between *LMNA* and *NTRK1*
6	36	F	Upper arm	Annular shiny raised pink papule melanoma or Spitz nevus	Spitz nevus	1.1	NA	*LMNA*	Deletion between *LMNA* and *NTRK1*
7	45	F	Leg	Pink papule; basal cell carcinoma, Spitz nevus, or irritated seborrheic keratosis	Spitz nevus	>0.9	No recurrence (5 y)	NA	Deletion between *LMNA* and *NTRK1*
8	50	F	Axilla	Irritated nevus	Spitz nevus	2	No recurrence (<1 y)	NA	NA
9	2	F	Upper arm	7×5 mm red papule present for 1 y that has become more raised over the last 1-2 mo.	Atypical Spitz tumor	0.5	NA	*LMNA*	Deletion between *LMNA* and *NTRK1*, loss of proximal 1p, loss of portions of 10q (not including *PTEN*), loss [illegible]portion of 16q
10									NA
11									[illegible]ozygous loss of [illegible]KN2A (by FISH)
12									[illegible]ion between *LMNA* [illegible]*NTRK1*, loss of
13									[illegible]tion of 1p, loss of 8p [illegible]zygous *CDKN2A* [illegible]tion (by FISH)
14					Spitz tumor			NA	Deletion between *LMNA* and *NTRK1*, loss of 9 and 13
15	17	M	Arm	5 mm growing, heterogeneously pigmented lesion	Atypical Spitz tumor	1.1	No recurrence (3 y)	NA	NA
16	19	F	Back	Hemangioma	Atypical Spitz tumor	1.2	No recurrence (6 y)	*LMNA*	Deletion between *LMNA* and *NTRK1*, gain of 13 and distal 17q
17	21	M	Ear	NA	Atypical Spitz tumor	1.9	NA	NA	NA
18	21	F	Upper arm	Irritated nevus	Atypical Spitz tumor	5.4	No recurrence (<1 y)	NA	NA
19	22	M	Back	8 mm, possible deep penetrating nevus	Atypical Spitz tumor	5.6	No recurrence (4 y)	NA	Deletion between *LMNA* and *NTRK1*
20	24	M	Elbow	6 mm nodule	Atypical Spitz tumor	1.1	Not available	NA	NA
21	28	F	Thigh	Pigmented papule	Atypical Spitz tumor	1.5	Not available	*LMNA*	Deletion between *LMNA* and *NTRK1*

年龄为2至63岁（中位年龄26岁），性别没有明显差异（男性占47%，女性占53%））。四肢多发（近端38%，远端15%），28%的肿瘤位于躯干上，15%位于头颈部。8例（21%），有近期有变化。12例（32%）无色素，9例（24%）与临床诊断有差异，包括非黑色素细胞病变，如黄色肉芽肿，基底细胞癌和血管瘤。

LMNA是最常见的融合伴侣（n = 13）

结果
RESULTS

TABLE 1. (*continued*)

Case	Age (y)	Sex	Site	Clinical Description	Final Diagnosis	Breslow Depth (mm)	Clinical Follow-up (Time)	Fusion Partner	Copy Number Aberrations
22	28	F	Back	Angiomatous nodule	Atypical Spitz tumor	3	Not available	NA	NA
23	30	M	Back	4 mm achromic Spitz	Atypical Spitz tumor	2.4	Not available	NA	NA
24	32	F	Arm	7 mm appeared in 3 mo	Atypical Spitz tumor	1.6	No recurrence (< 1 y)	*TP53*	NA
25	33	F	Back	Angioma	Atypical Spitz tumor	2.6	NA	*LMNA*	Deletion between *LMNA* and *NTRK1*
26	34	M	Wrist	Achromic with red halo	Atypical Spitz tumor	1.3	No recurrence (2 y)	NA	NA
27	36	M	Upper back	8 mm crescent-shaped pink and brown papule	Atypical Spitz tumor	0.6	NA	*LMNA*	Deletion between *LMNA* and *NTRK1*
28	36	M	Back	Circular, raised, changing colors, crusting and occasionally bleeding	Atypical Spitz tumor	2.3	NA	NA	Deletion between *LMNA* and *NTRK1*, loss of proximal 7q
29	36	M	Arm	NA	Atypical Spitz tumor	1.1	No recurrence (2.5 y)	NA	NA
30	37	M	Thigh	Nodule present for a few years, patient is phototype 4	Atypical Spitz tumor	2.4	NA	NA	Deletion between *LMNA* and *NTRK1*, gains of portions of 7p and 7q
31	39	F	Knee	Inflamed nevus, r/o melanoma	Atypical Spitz tumor	1.3	No recurrence (< 1 y)	NA	NA
32	44	M	Thigh	Achromic wart	Atypical Spitz tumor	2.1	No recurrence (3 y)	NA	NA
33	46	F	Forearm	4 mm, hyperpigmented	Atypical Spitz tumor	0.8	No recurrence (3 y)	NA	NA
34	63	F	Thigh	Possible basal cell carcinoma or Merkel cell carcinoma	Atypical Spitz tumor	1.8	NA	*LMNA*	Deletion between *LMNA* and *NTRK1*
35	36	F	Thigh	Flesh colored lesion	Spitzoid melano-ma	6.1	NA	*TPM3*	Homozygous *CDKN2A* deletion (by FISH)
36	17	F	Dorsal foot	NA	Spitzoid melano-ma	1.6	No recurrence (6 y)	*LMNA*	Deletion between *LMNA* and *NTRK1*, loss of 1p and 9, gain of proximal 1q including *LMNA-NTRK1* fusion
37	18	F	Thigh	NA	Spitzoid melano-ma	2.3	NA	*LMNA*	Deletion between *LMNA* and *NTRK1*, loss of 6p and 16q, gain of distal 20q
38	43	M	Hand	NA	Spitzoid melano-ma	3.5	No recurrence (2.5 y)	NA	Deletion between *LMNA* and *NTRK1*, gain of 1q including LMNA-NTRK1 fusion

恶性Spitz
肿瘤
4例
11%

结果
RESULTS

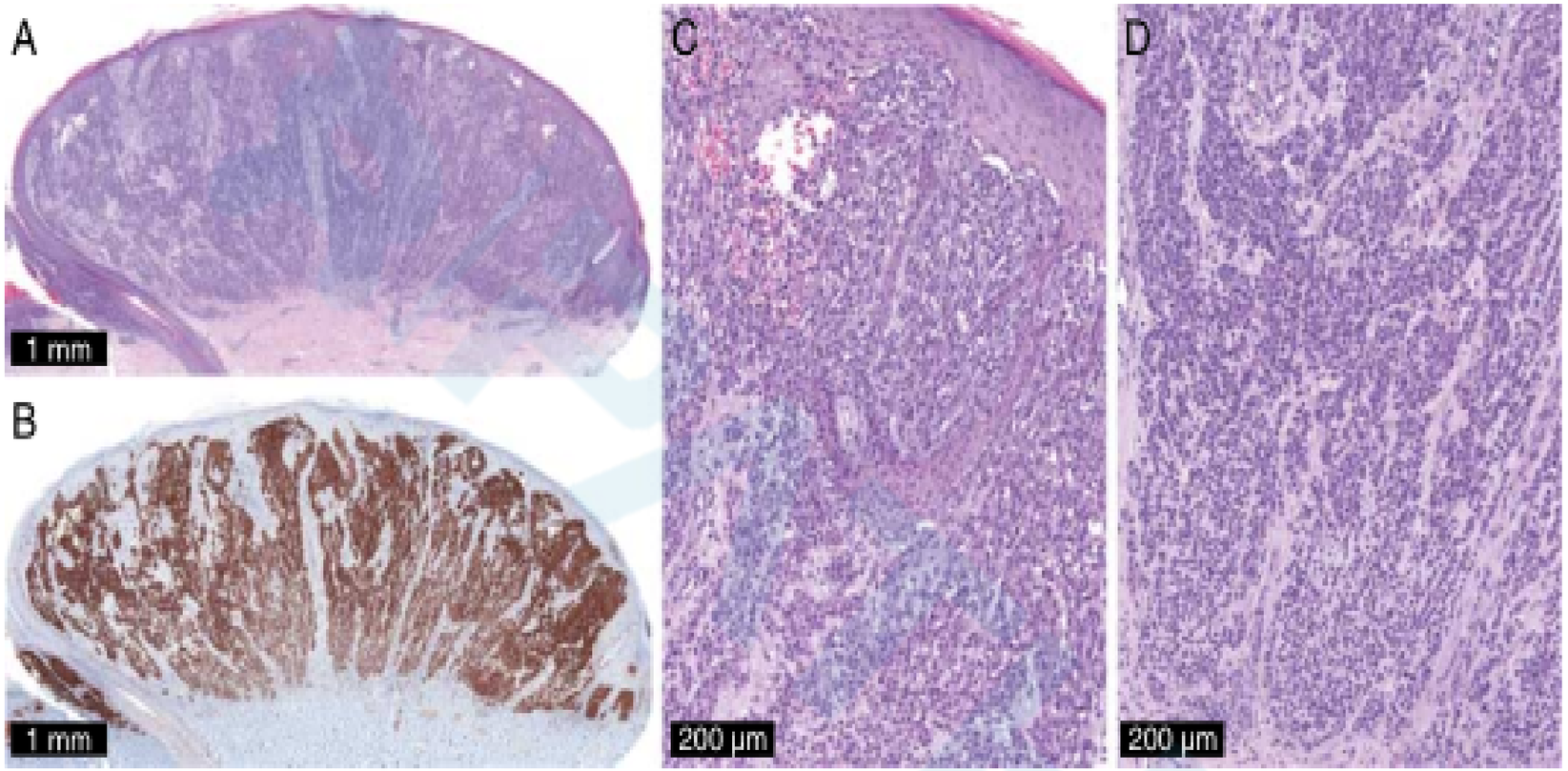

FIGURE 1. Atypical Spitz tumor with *NTRK1* fusion. At low magnification, hematoxylin and eosin staining (A), the exophytic profile with a flat lower border is apparent (case 28). The melanocytes demonstrate strong and uniform cytoplasmic expression of NTRK1 by immunohistochemistry (B). There is epidermal hyperplasia with filigree-like, thin, and branched rete (C). At the base of the tumor (D), neoplastic melanocytes display small hyperchromatic nuclei and scant cytoplasm.

结果
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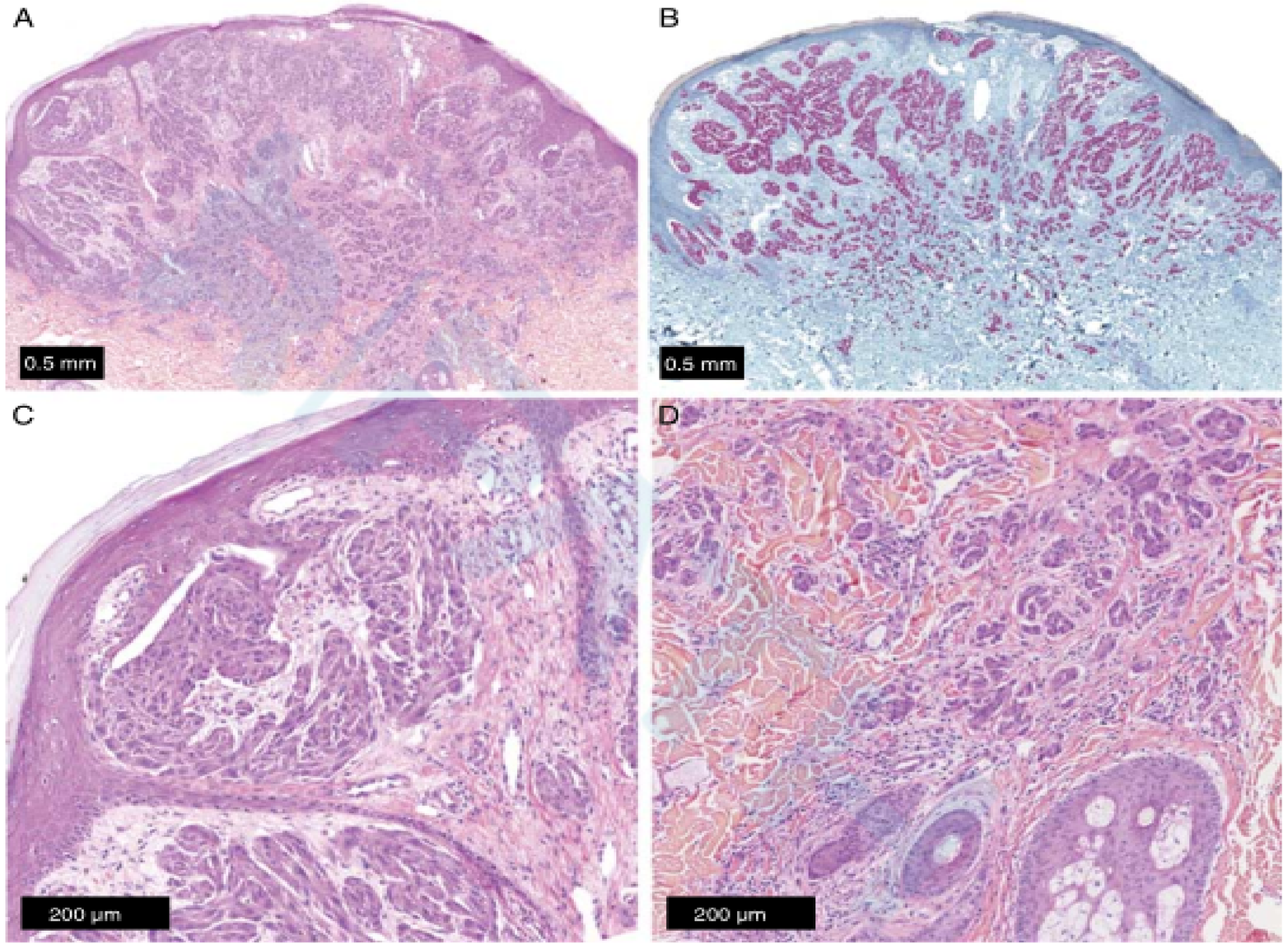

FIGURE 2. Atypical Spitz tumor with *NTRK1* fusion. At low power, hematoxylin and safranin staining (A) the tumor is exophytic with a wedge-shaped silhouette. There is diffuse and strongly expression of NTRK1 by immunohistochemistry (B). At higher power (C) filigree-like rete ridges which are long, thin, and branching are present. In the deep portion of tumor (D), there is marked maturation with smaller melanocytes and smaller and more dispersed clusters of melanocytes.

结果
RESULTS

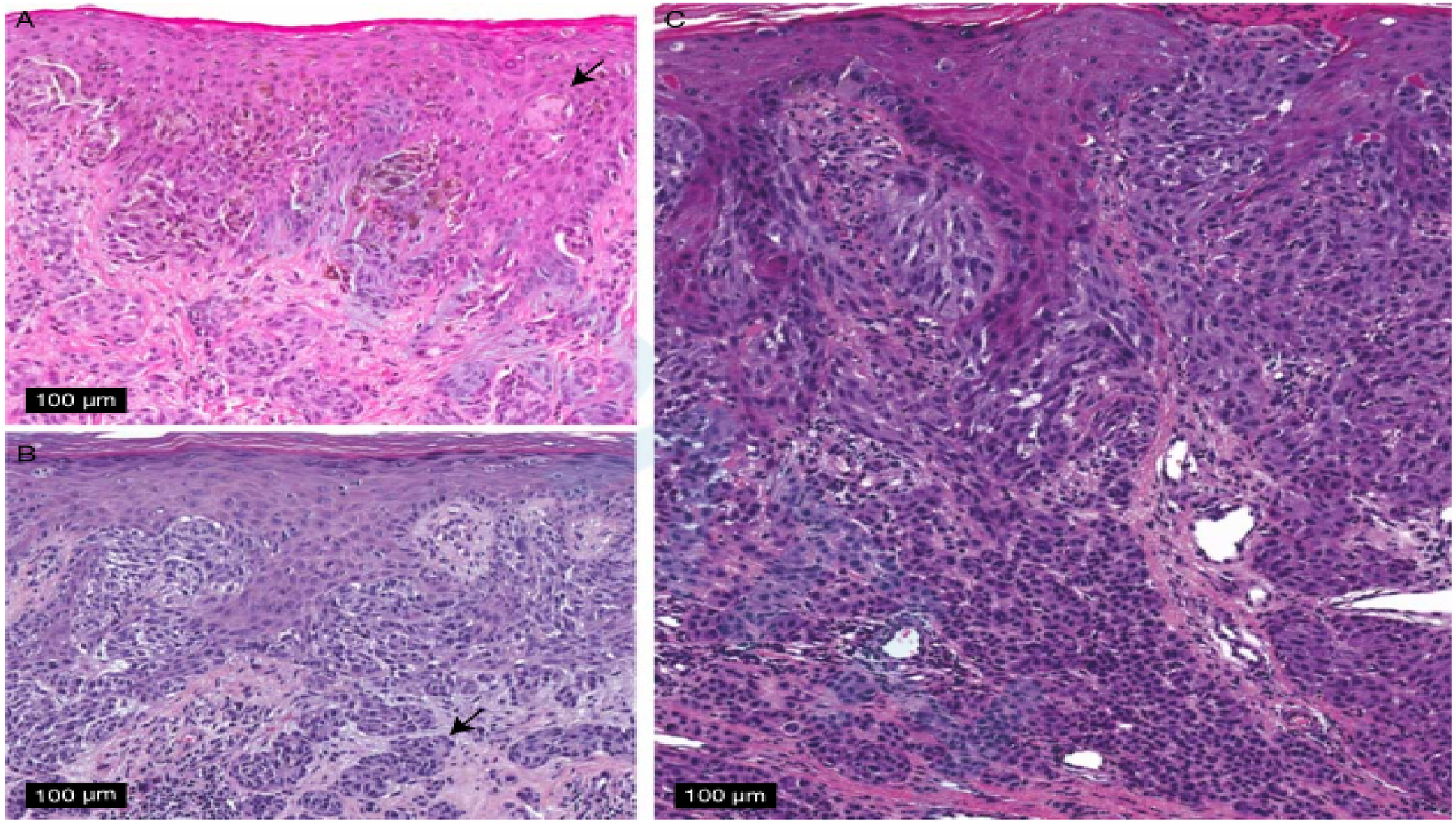

FIGURE 3. Epidermal hyperplasia, pagetoid scatter and Kamino bodies in Spitz tumors with *NTRK1* fusion. In case 4, hematoxylin and safranin staining (A), there are melanocytes in the upper levels of the epidermis as well as Kamino bodies (arrow). In case 7, hematoxylin and eosin staining (B), epidermal hyperplasia with filigree-like rete ridges is present. Lobulated nests with rosette-like structures are present in the dermis below (arrow). In case 16, hematoxylin and eosin staining (C) a large nest of melanocytes spans the epidermis below inflamed parakeratosis. Marked maturation of melanocytes is observed with large fusiform melanocytes at the junction and small melanocytes with scant cytoplasm at the base.

结果
RESULTS

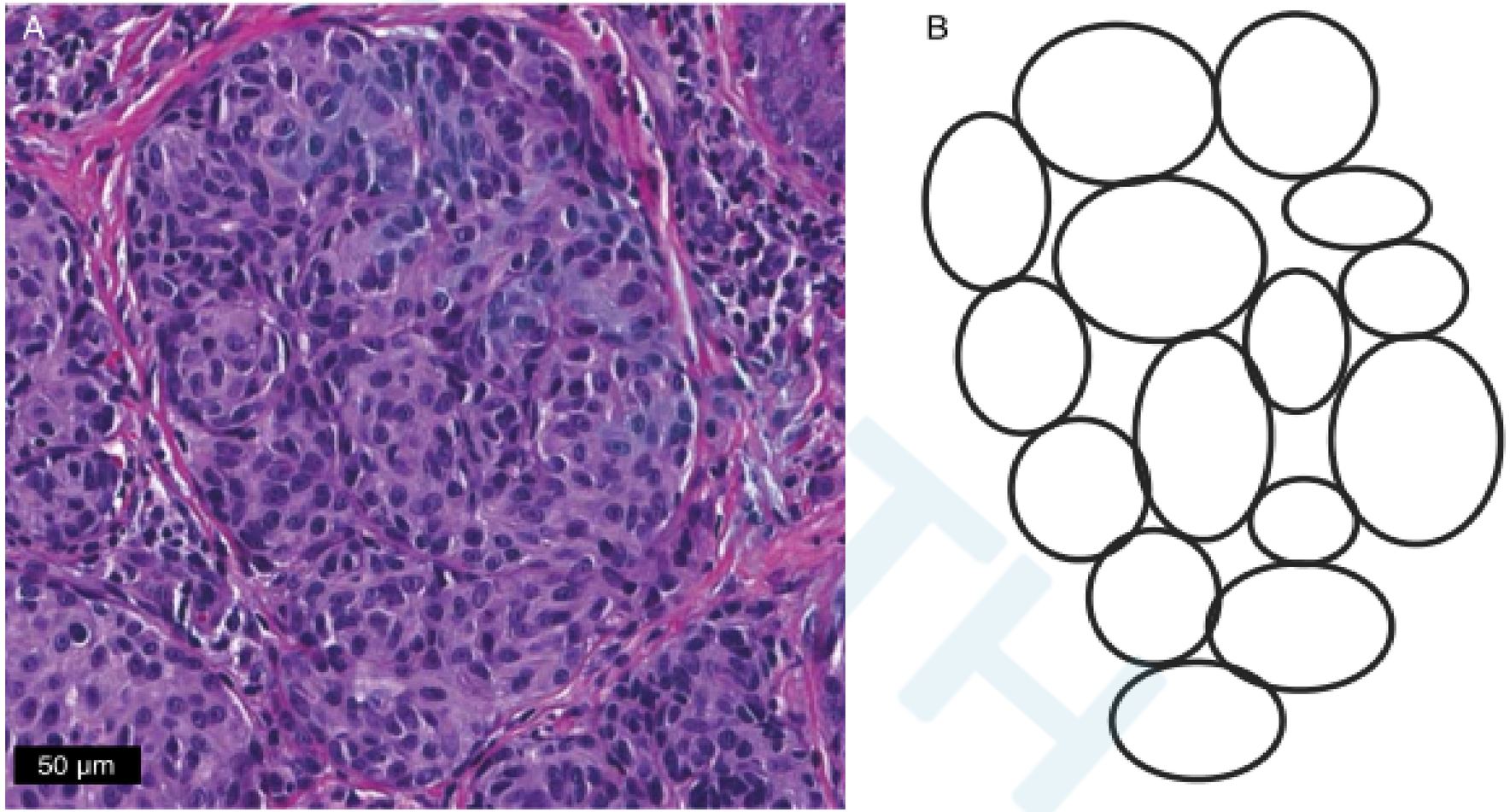

FIGURE 4. Lobulated nests in Spitz tumors with *NTRK1* fusion. A large lobulated nest from case 7 (A), accompanied by a diagram highlighting the internal small nests within (B).

结果
RESULTS

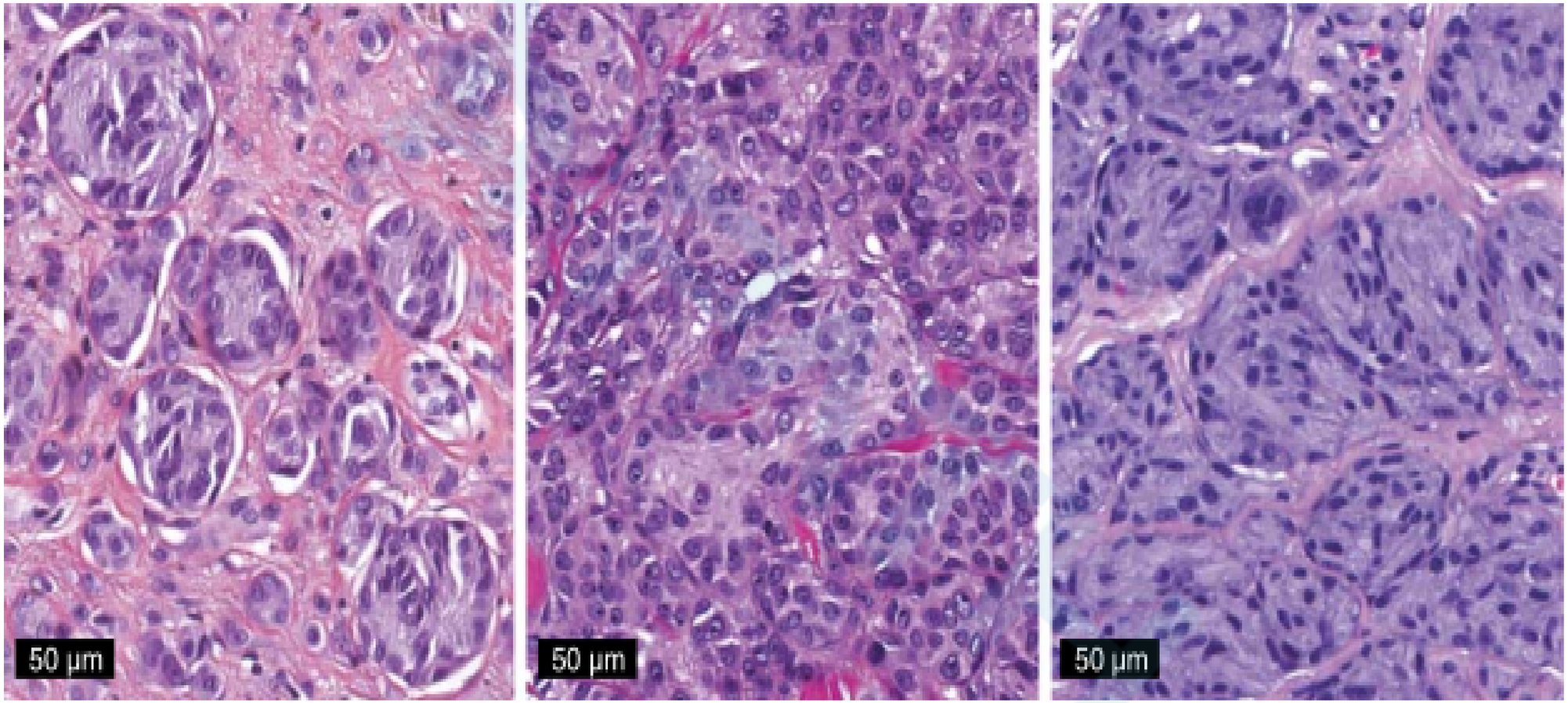

FIGURE 5. Rosette-like structures in Spitz tumors with *NTRK1* fusion. From left to right: case 30, case 37, case 14.

结果
RESULTS

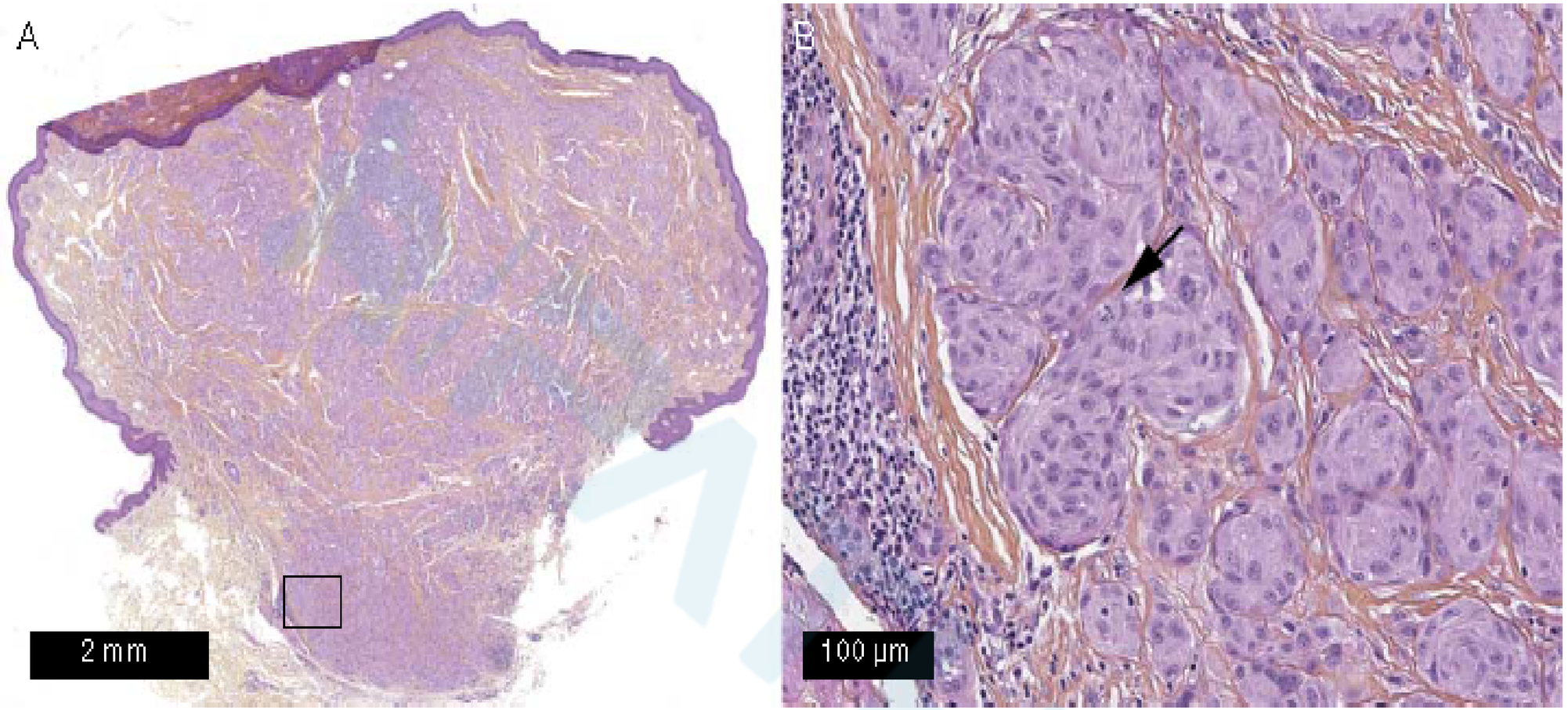

FIGURE 6. Malignant Spitz tumor with *NTRK1* fusion. Low power view, hematoxylin and safranin staining (A) demonstrates exophytic tumor with bulbous lower border and little maturation (case 35). High power view (B) of area outlined in (A) demonstrates a deep marginal mitosis (arrow).

结果
RESULTS

TABLE 2. Summary of Histopathologic Features of Spitz Tumors With *NTRK1* Fusion

	n/N (%)			
	Spitz Nevus	**Atypical Spitz Tumor**	**Spitz Melanoma**	**All**
Silhouette				
Exophytic	7/8 (88)	23/26 (88)	4/4 (100)	34/38 (89)
Tumor base				
Flat base	4/7 (57)	12/23 (52)	1/4 (25)	17/34 (50)
Wedge-shaped base	3/7 (43)	8/23 (35)	2/4 (50)	13/34 (38)
Bulbous base	0/7 (0)	2/23 (9)	2/4 (50)	4/34 (12)
Epidermal changes				
Hyperplasia	8/8 (100)	4/26 (15)	1/4 (25)	31/38 (82)
Filigree-like rete ridges	8/8 (100)	17/26 (65)	0/4 (0)	25/38 (66)
Consumption	1/8 (13)	4/26 (15)	1/4 (25)	6/38 (16)
Ulceration	1/8 (13)	4/26 (15)	1/4 (25)	6/38 (16)
Characteristics of junctional component				
Junctional nests present	8/8 (100)	21/26 (81)	3/4 (75)	32/38 (84)
Kamino bodies	5/8 (63)	10/26 (38)	0/4 (0)	15/38 (39)
Pagetoid scatter	3/8 (38)	6/26 (23)	1/4 (25)	10/38 (26)
Architecture				
Lobulated nests	6/8 (75)	18/25 (72)	4/4 (100)	28/37 (76)
Large superficial sheets/nests	5/8 (63)	19/26 (73)	2/4 (50)	26/38 (68)
Adnexal extension	3/7 (43)	12/24 (50)	2/3 (67)	17/34 (50)
Maturation to common nevus cytomorphology	6/8 (75)	10/25 (40)	1/4 (25)	17/37 (46)
Rosette-like structures	2/8 (25)	6/26 (23)	3/4 (75)	11/38 (29)
Peripheral infiltrative pattern	2/7 (29)	7/23 (30)	1/3 (33)	10/33 (30)
Fascicular growth pattern	1/8 (13)	4/25 (16)	0/4 (0)	5/37 (14)
Cytologic features				
Clefts between melanocytes	6/8 (75)	18/26 (69)	3/4 (75)	27/38 (71)
Multinucleated melanocytes	4/8 (50)	15/26 (58)	3/4 (75)	22/38 (58)
Cytoplasmic pigmentation	2/8 (25)	14/26 (54)	1/4 (25)	17/38 (45)
Large nuclei with prominent nucleoli	1/8 (13)	12/26 (46)	2/4 (50)	15/38 (39)
Mixed spindled and epithelioid cytomorphology	6/8 (75)	17/26 (65)	3/4 (75)	26/38 (68)
Pure epithelioid cytomorphology	2/8 (25)	6/26 (23)	1/4 (25)	9/38 (24)
Pure spindled cytomorphology	0/8 (0)	3/26 (12)	0/4 (0)	3/38 (8)
Other				
Desmoplastic stroma	2/8 (25)	8/26 (31)	2/4 (50)	12/38 (32)
Dermal mitoses	3/8 (38)	14/25 (56)	4/4 (100)	21/37 (57)
Permeative lymphocytic infiltrate	2/8 (25)	6/26 (23)	0/4 (0)	8/38 (21)

外生性89%

平坦基底50%
楔形基底38%
球根基底12%

细丝状的网状脊

分叶状的巢

痣细胞的成熟
玫瑰花环结构

混合的梭形细胞
上皮样细胞

04 讨论
DISCUSSION

讨论
DISCUSSION

NTRK1基因

NTRK1、NTRK2、NTRK3都是受体酪氨酸激酶Trk家族的成员，分别负责编码TRKA、TRKB 和 TRKC 的合成

神经营养因子与TRK 蛋白质结合后可诱导受体二聚体化、磷酸化并激活下游PI3K、RAS/MAPK/ERK和PLC- γ 的信号级联通路

TRK信号通路的改变，包括基因融合、蛋白过度表达或单核苷酸改变，已经被发现是许多肿瘤的致病原因，特别是NTRK基因的融合，是目前最明确的致癌原因

讨论
DISCUSSION

NTRK1和NTRK3在黑色素细胞中表达并介导神经营养因子的调节

具有NTRK1和NTRK3融合的黑色素肿瘤显示出明显的组织病理学特点

一种含较多色素和梭形细胞的变异型Spitz痣，也称为**色素性梭形细胞痣（Reed痣）**，大多数具有NTRK3融合，而没有NTRK1融合。这表明NTRK1和NTRK3融合可能导致不同的下游信号通路

NTRK1和NTRK3可导致下游途径的激活，包括MAPK，PI3-K和PLC-γ途径

讨论
DISCUSSION

NTRK1基因

NTRK基因融合在大多数肿瘤中只占据了0.5%-1%，在某些罕见肿瘤中占比较高，比如在唾液腺癌、乳腺分泌性癌、婴儿纤维肉瘤及先天性中胚叶肾瘤中，可达90%以上

NTRK融合在肿瘤发生早期就会出现，并在肿瘤生长和扩散过程中持续存在

相关靶向药物有克唑替尼、Entrectinib

讨论
DISCUSSION

该研究评估了一组具有NTRK1融合的Spitz肿瘤，并确定了这种遗传亚型的一些形态学特征

在近三分之一的NTRK1融合肿瘤中观察到的玫瑰花结样结构

先前的研究估计，8%的Spitz肿瘤具有NTRK1融合，玫瑰花环样结构特异的存在于该类型肿瘤中

与其他遗传表型的Spitz肿瘤相比，具有细丝状的网状脊和真皮内黑色素细胞明显成熟的NTRK1融合的Spitz肿瘤对表皮生长因子的依赖性增加

总结
summary

具有NTRK1融合的Spitz肿瘤中常见细丝状的网状脊、分叶状的巢、玫瑰花环结构和成熟现象

独特的组织病理学特征在具有NTRK1融合的Spitz肿瘤中可以帮助判断分子测试的优先次序，以便更有效的指导靶向治疗。

THANK YOU

感谢聆听，批评指导