
The expanding galaxy of "Spitz nevi"
From the perspective of conventional dermatopathology
Lorenzo Cerroni & Livia Cerroni

Sophie Spitz (1910-1956)

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VOLUME XXIV

1948

MELANOMAS OF CHILDHOOD *

SOPHIE SPITZ, M.D.

(From the Pathology Laboratories of the Memorial Hospital, New York, N.Y.)

It has become apparent over a period of years that even when a histologic diagnosis of malignant melanoma has been made in children the clinical behavior rarely has been that of a malignant tumor. The disparity in behavior of the melanomas of adults and children, despite the histologic similarity of the lesions occurring in the different age groups, is obviously a matter of fundamental importance and the following questions immediately arise: Does the histologically malignant melanoma of children differ in any structural detail from that of adults? Can the clinical behavior of these lesions be predicted from their histologic structure? What, if any, are the factors known to influence the clinical behavior? Should the melanomas of children be treated any differently from the melanomas of adults?

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In a search of the files of the Memorial Hospital for instances of malignant melanoma in children, it soon became apparent that the diagnosis had been made with far greater frequency 20 or more years ago than in the past decade. This difference was quickly accounted for in the usual structure of the benign pigmented nevi of children as contrasted with that of the benign nevi of adults. In more recent years, the criteria for the diagnosis of malignant melanoma had become clarified to the extent that histologic features of the nevus of childhood, formerly regarded as stigmata of malignant change, were no longer so considered. However, there remained a group of cases in which a diagnosis of malignant melanoma seemed histologically sound. Over a period of years, the qualification has been added to reports of such lesions that they probably would not behave as malignant tumors. In order to distinguish these lesions both from the malignant melanoma of adults and the unequivocally benign nevus of childhood, the term "juvenile melanoma" has been adopted. The term "melanoma" in this paper, as in common usage, has been applied only as an abbreviation for malignant melanoma.

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* Received for publication, June 4, 1947.
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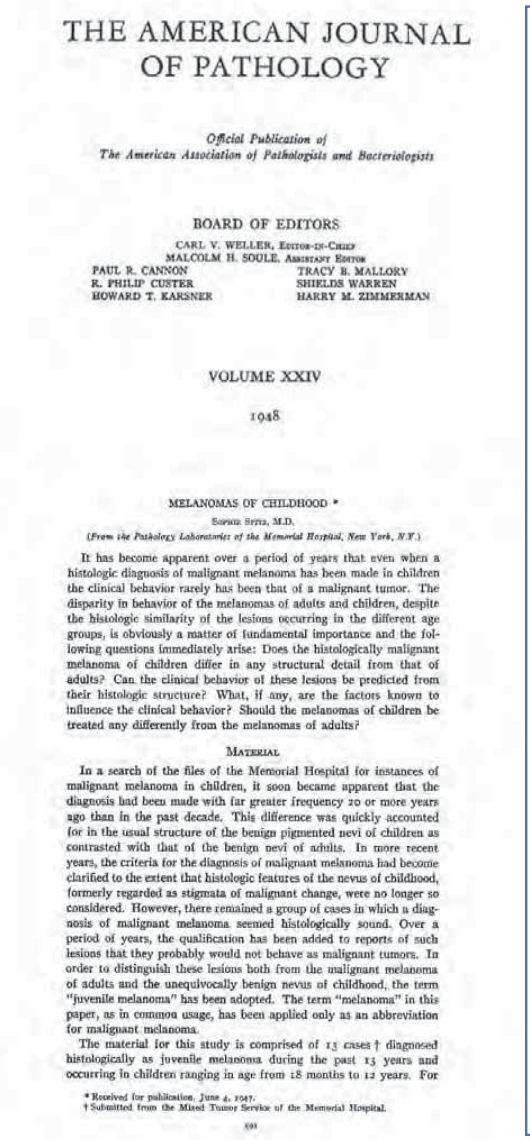

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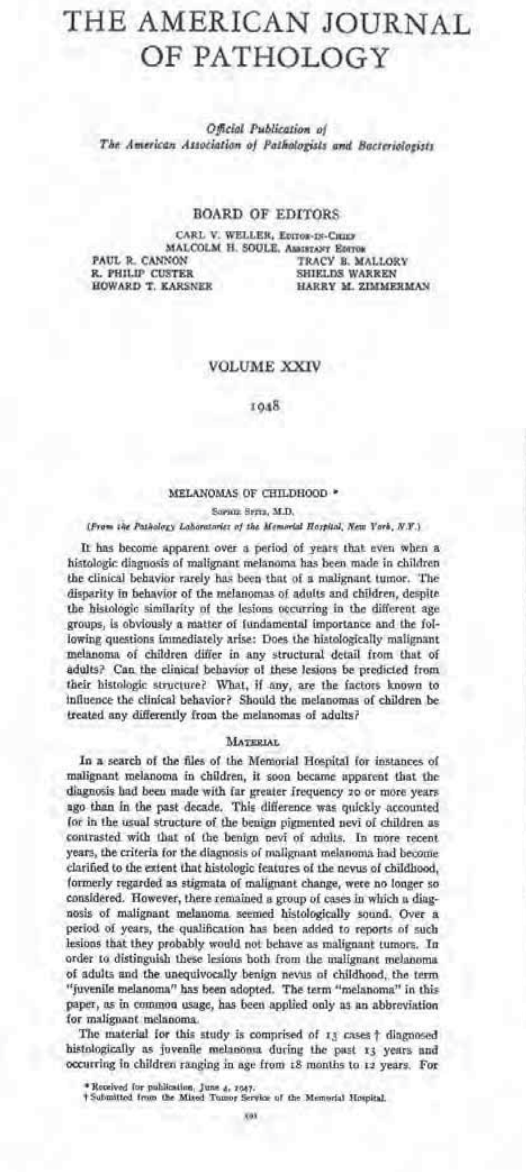

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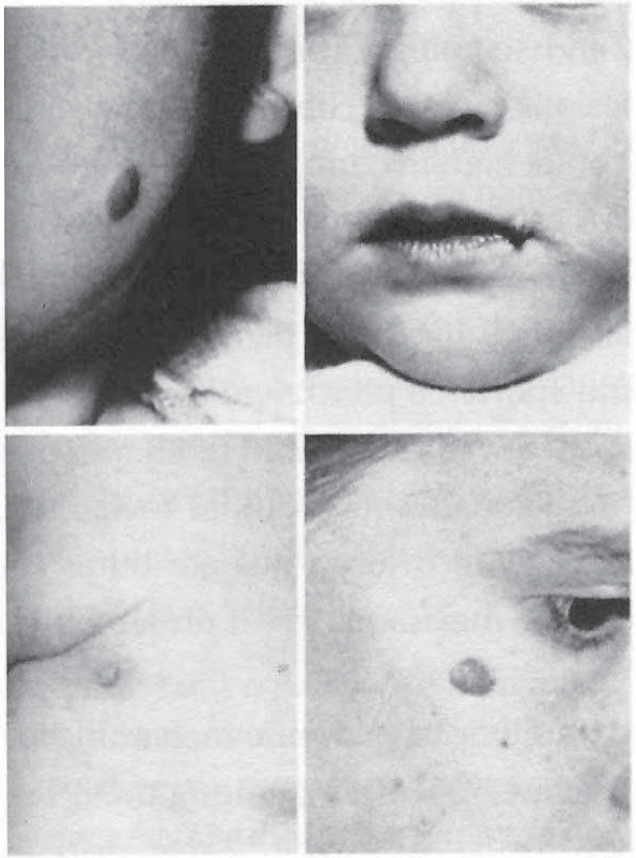

13 patients (M:F=5:8);
age range: 18 months – 12 years

"One of the 13 cases had been clinically malignant and the child is dead."

Control group of "conventional" melanoma of adults:
17 patients (M:F=5:12);
age range **14 – 19 years** (12 DoD)

"There is a precipitous rise in the capacity of melanomas to metastasize after puberty despite the histologic similarity to the usually non-metastasizing juvenile melanoma."

MELANOMAS OF CHILDHOOD *

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One of the 13 cases had been clinically malignant and the child is dead. This lesion occurred on the sole of the foot but was not described as involving the skin. After rapid growth over a period of 6 weeks, a soft white tumor, 2 cm. in diameter, was resected from the plantar fascia.

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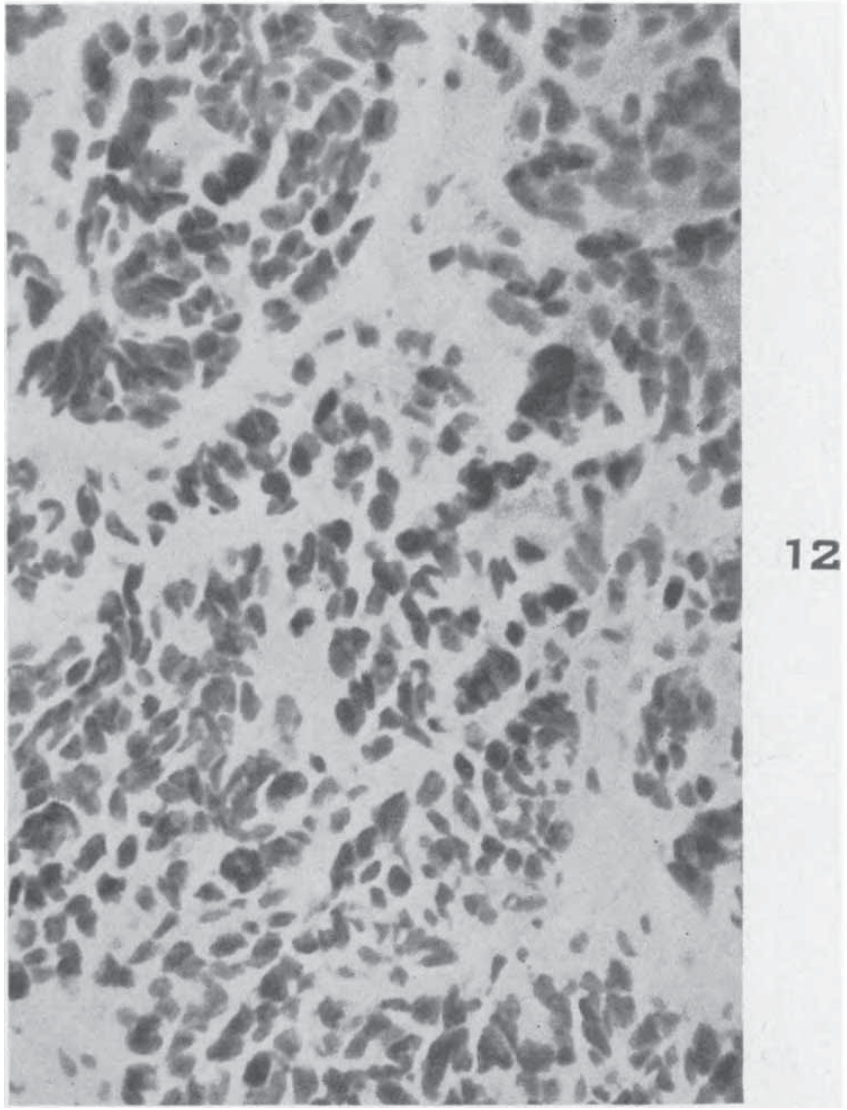

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FIG. 12. Spindle cell structure in a fatal case of juvenile melanoma (female, 12 years old; death 4 months after local excision). Hematoxylin and eosin stain. × 180.

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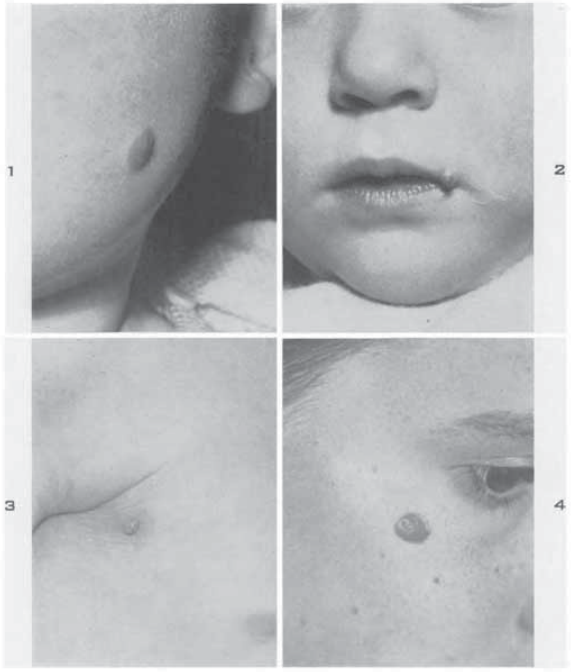

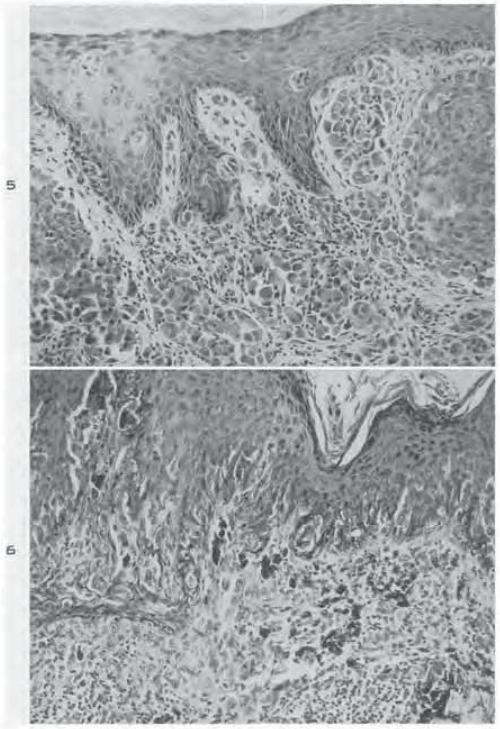

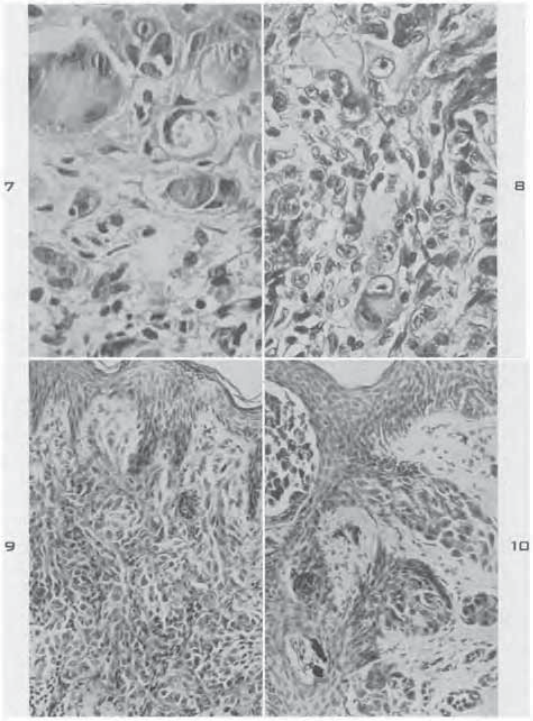

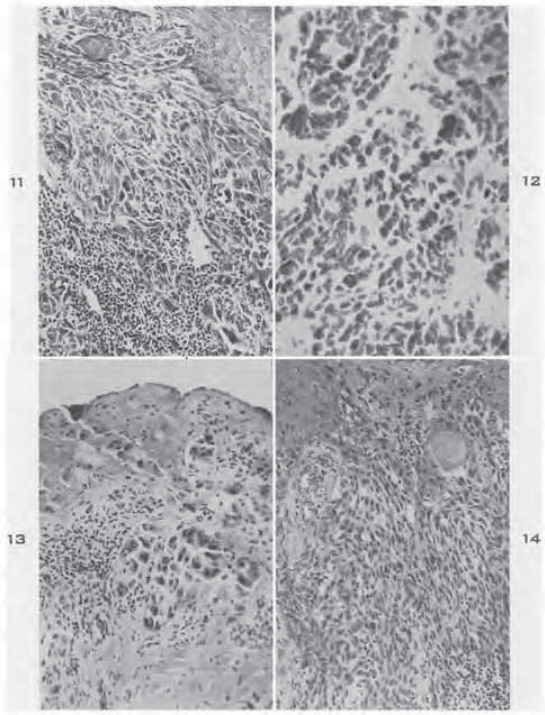

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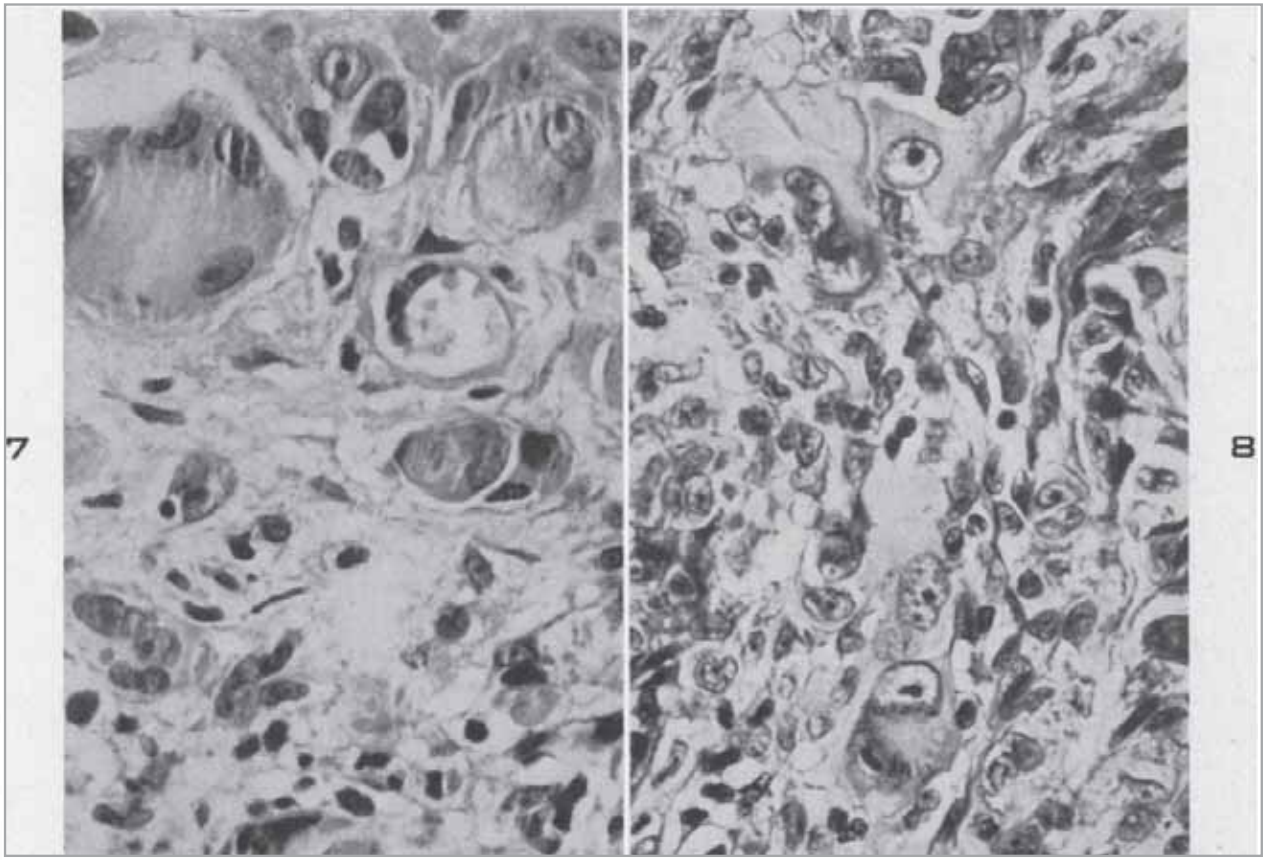
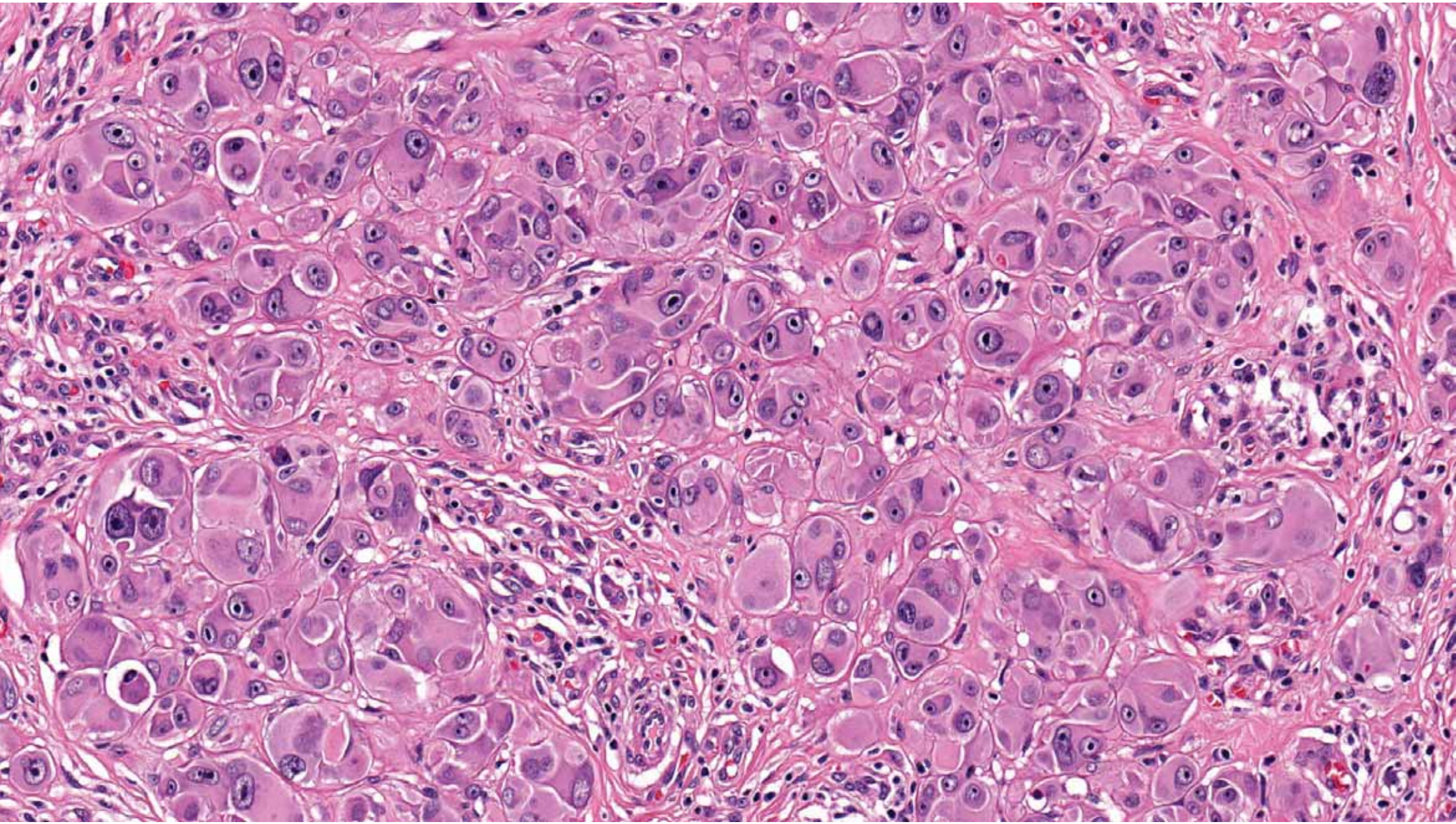
"In general, it was concluded that differentiation histologically between the juvenile and adult melanomas could not be made with certainty in most cases. The one feature, found in almost one-half the cases of juvenile melanoma, that seemed to permit a histologic distinction from adult melanoma, was the presence of giant cells (Figs. 7 and 8)."



"The juvenile melanoma may be distinguished histologically from adult melanoma in about one-half the cases by the presence of giant cells in the former which seldom occur in the latter."



TUMORS OF THE SOFT SOMATIC TISSUES IN INFANCY AND CHILDHOOD

GEORGE T. PACK, M.D., AND THOMAS J. ANGLEM, M.D.
NEW YORK, N. Y.

TUMORS are extremely rare in the early years of life with the exception of those which occur more specifically during that period. In comparison with similar tumors in older persons, cancers in the young are more rapidly growing, highly cellular, undifferentiated, anaplastic neoplasms of greater malignancy.

From Jan. 1, 1917, to Oct. 1, 1938, at the Memorial Hospital, New York, there were one hundred patients under 16 years of age with tumors of the soft parts, excluding the majority of those on the head and neck.

Sarcoma of the soft parts in children is not encountered to any considerable degree, according to reports in the literature. Among all cases admitted to the Radiation Service at Bellevue Hospital, New York, from 1924 to 1934, Kaplan and Rubenfeld found 78 soft tissue sarcomas, exclusive of those in the eye, lymphosarcoma, and Kaposi's disease. In only four instances were the patients under 16 years of age—2, 5, 13, and 15 years, respectively.

Since our figures cover a long period, nearly twenty-two years, in a hospital devoted solely to the treatment of cancer and allied diseases, it may be concluded that such tumors are rare in early life.

TABLE I

DISTRIBUTION ACCORDING TO TYPE OF TUMOR

TYPE OF TUMOR	NUMBER	PER CENT
A. Malignant Tumors		
Total	58	100.0
1. Neurogenic sarcoma	23	39.7
2. Neurocytoma	1	1.7
3. Liposarcoma	13	22.4
4. Rhabdomyosarcoma	2	3.4
5. Sarcoma unclassified	10	17.2
6. Melanoma	7	12.1
7. Malignant synovioma	1	1.7
8. Granulation cell sarcoma	1	1.7
B. Benign Tumors		
Total	42	100.0
1. Neurofibroma	10	23.8
2. Lipoma	11	26.2
3. Naevus (melanotic)	17	40.4
4. Glomus tumor	1	2.4
5. Xanthoma or benign giant-cell tumor of tendon sheath	2	4.8
6. Teratoid tumor	1	2.4

Part of a Symposium on Tumors of Childhood, New York Academy of Medicine, Section on Pediatrics, Dec. 9, 1937.

From the Mixed Tumor Service of the Memorial Hospital for Cancer and Allied Diseases, New York, N. Y.

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J Pediatr 1939;15:372-400

"Although malignant melanomas are found in infancy and childhood, they are of low-grade malignancy and seldom metastasize. Under the microscope these tumors may be indistinguishable from other melanomas occurring in adult life which exhibit a high degree of malignancy by diffuse metastasis, so that the pathologist, on microscopic examination, may term them melanomas, yet their behavior is not in keeping with their morphologic structure."

A REORIENTATION ON THE HISTOGENESIS AND CLINICAL SIGNIFICANCE OF CUTANEOUS NEVI AND MELANOMAS*

ARTHUR C. ALLEN, M.D.

FEW will question that of all the tumors of skin, the pigmented lesions are probably the most frequently misdiagnosed.[2] The errors are in two directions: The benign nevi are often called malignant and the malignant melanomas are in many instances considered benign. The gravity of either error is obvious; the basis for the errors is less obvious although clearly worth studying.

For reasons to be elaborated, it now seems likely that the ultimate source of a great many of the diagnostic difficulties stems from insecure and, what is perhaps more to the point, impractical morphogenetic information that hence cannot be applied effectively in the day-to-day diagnosis of the pigmented lesions. It is true that very often the understanding of the morphogenesis of a neoplasm is not a requisite for the accurate judgment

reflect a more serious error in fundamental concept, still remains to be shown. The problem is immensely complicated and it need not be mentioned that the service rendered by the classical contributions to the neurogenic theory remains established. Nevertheless it would be unwise to deny that there has developed a nimbus of mysticism and authoritativeness around this theory that possibly has served to dissuade inquiry by troubled pathologists.

The basic issue is briefly this: Does the malignant melanoma originate from the common mole? The clarity and validity of the answer to this question are directly dependent on the evidence that is offered with regard to the histogenesis of a variety of pigmented cutaneous tumors.

Actually there is noteworthy evidence to

small measure the difficulties attending the diagnosis, especially of the early melanoma where a possibility of salvage of patients exists. Toward this end, it will be necessary to define the somewhat confused terminology of the histological variants of nevi, to review the gen-

From the Department of Pathology, Memorial Hospital, New York, N. Y.

* The material on which this paper is based was studied at The New York Memorial Hospital for the Treatment of Cancer and Allied Diseases and The Army Institute of Pathology (Dermal Registry).

Received for publication, May 3, 1948.

"There is a group of lesions occurring before puberty which, despite their having the histological characteristics of melanomas, do not behave as malignant lesions."

Cancer, 1949;2:28-56

MALIGNANT MELANOMA

A Clinicopathological Analysis of the Criteria for Diagnosis and Prognosis

ARTHUR C. ALLEN, M.D., AND SOPHIE SPITZ, M.D.

WE PREVIOUSLY PRESENTED EVIDENCE that was intended primarily to clarify in a practical, workable manner the criteria for the histological diagnosis of nevi, juvenile melanomas, and malignant melanomas.[2, 3, 4, 19, 20] This was done because it appeared that the recondite histogenetic concepts then in vogue had not measurably supplied the answers to what the pathologist needed to know in order to be able to state confidently that a given lesion, particularly the small one, was or was not malignant. Accordingly, we defined in detail the clinical and histological features of the melanocarcinoma and of each of the several varieties of nevi. From these details there was acuminated a set

ty.[2, 19, 20] In addition, because it was apparent that several of the lesions were not autochthonous but, rather, represented a stage in the evolution of the junctional nevi, a histogenetic concept embodying this relationship was outlined.[2] In accordance with this concept, the junctional nevi, the intradermal nevi, the juvenile melanomas, and the melanocarcinomas of both skin and mucous membranes are of epithelial rather than of neural origin.

These, then, represented the broad principles of our concepts of the histogenesis and the diagnostic criteria of the nevi and melanocarcinomas, impressions that were derived from a

We classify the lesions as follows:

A. Benign

1. Intradermal nevus (common mole)
2. Junctional nevus
3. Compound nevus
4. Juvenile melanoma
5. Blue (Jadassohn-Tieche) nevus

7. That, for this reason, when feasible, moles in these three locations should be prophylactically excised, preferably prior to puber-

omit further discussion of the histogenesis of these lesions for the time being, except to state that nothing we have observed in this material —or in the literature—has in any degree repudiated the validity of the concepts previously outlined.[2, 19] Finally, with regard to the use of the

From the Pathological Laboratories, Memorial Center for Cancer and Allied Diseases, New York, New York.

Received for publication, July 14, 1952.

Cancer 1953;6:1-45

Review Article

Nevus of Large Spindle and/or Epithelioid Cells (Spitz's Nevus)

Cleire Paniago-Pereira, MD; John C. Maize, MD; A. Bernard Ackerman, MD

• By now it is well recognized that there is a benign melanocytic nevus, common in the young and common enough in adults, that has histological features that are confusable with those of malignant melanoma. The anomaly is usually referred to as benign juvenile melanoma, sometimes as Spitz's nevus, and, by some histopathologists, as spindle and epithelioid cell nevus. All the histological subtleties and variations of the condition are still not fully appreciated and some of them are still being misinterpreted as those of malignant melanoma.

We herewith present a study designed to clarify the issues and offer firm criteria for histological differentiation of the nevus in point from malignant melanoma.

We also suggest a new name for it and supporting arguments therefor.

(*Arch Dermatol* 114:1811-1823, 1978)

This is a study of the histological features of 200 specimens of that distinctive melanocytic nevus, which was originally designated juvenile melanoma by Spitz, collected during a three-year period in the Dermatopathology Laboratory of the New York University Medical Center. To us, the term "nevus of large spindle and/or epithelioid cells" is most informative because it describes and emphasizes those microscopic characteristics that differentiate this nevus from all other melanocytic nevi and from malignant melanoma.

Accepted for publication Aug 7, 1978.

From the Departments of Dermatology (Drs Paniago-Pereira, Maize, and Ackerman), and Pathology (Dr Ackerman), New York University School of Medicine, New York. Dr Maize is now with University of Buffalo School of Medicine, and Dr Pereira is with The City Hospital, Brazilia, Brazil.

Reprint requests to Dermatopathology Section, Skin and Cancer Unit, New York University Medical Center, 562 First Ave, New York, NY 10016 (Dr Ackerman).

Thirty-nine percent of the nevi came from patients who were less than 14 years of age; 61% were from persons older than age 14. The youngest patient in this series was 13 months old; the oldest was 69 years old. The most common locations for the nevus of large spindle and/or epithelioid cells were the head and legs. The legs were sites of predilection for the lesions in women.

We have classified the nevus of large spindle and/or epithelioid cells by histological patterns and by cell types. By pattern, they were found to be junctional in 9.5% of the cases, compound in 66%, and intradermal in 24.5%. By cell type, they were predominantly spindle shaped in 54.5% of all cases, predominantly epithelioid in 21%, or a combination of both cell types in 24.5%. Some histological variants were found and described as granulomatous, lichenoid, and desmoplastic. Specimens that were sessile and papillomatous with prominent telangiectasias, severe edema of the dermis, and containing "acantholytic" epithelioid cells and scant melanin were identifiable as coming from young children; those that were dome shaped and associated with isolated large spindle and/or epithelioid cells in a markedly fibrotic dermis were considered to be from adults.

An attempt has been made to establish histological criteria for the recognition of every pattern and type of nevus of large spindle and/or epithelioid cells and for differentiating them from malignant melanomas. These criteria have been categorized according to importance as major and minor features. The major features of nevus of large spindle and/or epithelioid cells are some unusually large cells, spindle and/or epithelioid cells, sharp lateral demarcation of the intraepidermal melanocytic component of the lesion (no horizontal extension of individual melanocytes), rare or sparse individual melanocytes high above the epidermal basal layer, and progressive maturation of nevus cells the deeper they lie in the dermis. Minor features, those that are found commonly enough but are not crucial for diagnosis, are telangiectasia, perivascular inflammatory cell infiltrates, epidermal hyperplasia, clefts between nests of melanocytes and surrounding epidermal keratinocytes, giant nevus cells, fibrosis, edema, and scanty melanin.

Finally, the most important reports about this nevus have been critically reviewed and differences of opinion have been brought into sharper focus.

HISTORICAL ASPECTS OF NEVUS OF LARGE SPINDLE AND/OR EPITHELIOID CELLS

In 1910, Darier and Civatte reported the case of an 8-month-old boy in whom a fast-growing, red nodule had developed on the nose that histologically showed what they interpreted to be nevus cells and fusiform cells.[1] Those renowned dermatologists, so expert in dermatopathology, were not able to decide, either from the clinical or the histological features, whether they were dealing with a benign or a malignant melanocytic lesion. During the years pathologists

Spitz's original term "juvenile melanoma" has been widely used. Because of the biologic benignity of the lesion, McWhorter and Woolner preferred the term "benign juvenile melanoma" and others subsequently adopted this name. Pack et al introduced the term "prepubertal melanoma" in 1947, and this designation was used again by Pack in later articles and also by other authors. Other terms that have been suggested are "juvenile melanoma of the epithelioid cell type", "spindle cell compound nevus", "Spitz tumor", "so-called juvenile melanoma", "pseudomelanoma", "naevus prominens et pigmentosus", "spindle cell, epithelioid cell and round cell juvenile melanoma", "nevus with large cells", and "melanoma of Spitz," or "tumor of Spitz of fusiform cell nevus."

SPINDLE AND EPITHELIOID CELL NEVI IN CHILDREN AND ADULTS

A Review of 211 Cases of the Spitz Nevus

D. WEEDON, FRCPA* AND J. H. LITTLE, FRCPA, FRCPATH†

A large series of 211 Spitz nevi is reviewed. 30% of the lesions were from patients 20 years of age and over. The trunk and lower extremity were most commonly involved. There were no significant histologic differences between cases from adults and children. Features which may help in differentiating atypical Spitz nevi from malignant melanoma include the presence of some nevus cell maturity at the base, an absence of atypical mitoses, no significant upward epidermal spread and the nuclear chromatin pattern.

Cancer 40:217–225, 1977.

THE SPITZ NEVUS (BENIGN JUVENILE MELANOMA, spindle epithelioid cell nevus) is a benign tumor, found predominantly in children and adolescents, which has some histologic resemblance to malignant melanoma.

During the study on melanoma by the Queensland Melanoma Project[6] (which showed that the northern Australian State of Queensland has the highest incidence of melanoma in the world of 16 cases per 100,000 population), it

METHODS

The cases examined were from the files of the Princess Alexandra Hospital, Brisbane, which included referrals to one of the pathologists (J.H.L.) of the Queensland Melanoma Project (Q.M.P.) and from the files of most of the pathology laboratories in Queensland. In all a total of 220 cases were examined, but on review, nine lesions were regarded as not being Spitz

lens or the naked eye. The descriptive terms used were flat or uneven, plateau-like or slightly elevated and polypoid or hemispherical. These

and to Dr. Neville Davis, Coordinator, Queensland Melanoma Project, for his continued support.

Accepted for publication October 25, 1976.

"The term Spitz nevus has been used in accordance with recommendations on nomenclature of a committee of Australian pathologists in 1967. This name gives credit to the late Sophie Spitz who firmly established the histologic criteria for the diagnosis of these tumors and avoids the confusion engendered by the word "melanoma" in the title "benign juvenile melanoma"."

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• By now it is well recognized that there is a benign melanocytic nevus, common in the young and common enough in adults, that has histological features that are confusable with those of malignant melanoma. The anomaly is usually referred to as benign juvenile melanoma, sometimes as Spitz's nevus, and, by some histopathologists, as spindle and epithelioid cell nevus. All the histological subtleties and variations of the condition are still not fully appreciated and some of them are still being misinterpreted as

those microscopic characteristics that differentiate this nevus from all other melanocytic nevi and from malignant melanoma.

Thirty-nine percent of the nevi came from patients who were less than 14 years of age; 61% were from persons older than age 14. The youngest patient in this series was 13 months old; the oldest was 69 years old. The most common locations for the nevus of large spindle and/or epithelioid cells were the head and

These criteria have been categorized according to importance as major and minor features. The major features of nevus of large spindle and/or epithelioid cells are some unusually large cells, spindle and/or epithelioid cells, sharp lateral demarcation of the intraepidermal melanocytic component of the lesion (no horizontal extension of individual melanocytes), rare or sparse individual melanocytes high above the epidermal basal layer, and progressive maturation of nevus

term "nevus of large spindle and/or epithelioid cells" is most informative because it describes and emphasizes

dermis, and containing acantholytic epithelioid cells and scant melanin were identifiable as coming from young children; those that were dome shaped and associated with isolated large spindle and/or epithelioid cells in a markedly fibrotic dermis were considered to be from adults.

An attempt has been made to establish histological criteria for the recognition of every pattern and type of nevus of large spindle and/or epithelioid cells and for differentiating them from malignant melanomas.

HISTORICAL ASPECTS OF NEVUS OF LARGE SPINDLE AND/OR EPITHELIOID CELLS

In 1910, Darier and Civatte reported the case of an 8-month-old boy in whom a fast-growing, red nodule had developed on the nose that histologically showed what they interpreted to be nevus cells and fusiform cells.[1] Those renowned dermatologists, so expert in dermatopathology, were not able to decide, either from the clinical or the histological features, whether they were dealing with a benign or a malignant melanocytic lesion. During the years pathologists

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From the Departments of Dermatology (Drs Paniago-Pereira, Maize, and Ackerman), and Pathology (Dr Ackerman), New York University School of Medicine, New York. Dr Maize is now with University of Buffalo School of Medicine, and Dr Pereira is with The City Hospital, Brazilia, Brazil.

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"In our opinion, "the nevus of large spindle and/or epitheloid cells" is the best histological descriptive term for the lesion under consideration and "Spitz's nevus" is an appropriate eponymic designation for historical purposes."

The term "Spitz nevus" was used colloquially in discussions at the microscope and in meetings in the US in the 60s.

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On 2 cases of Spitz-Allen compound nevus (so-called juvenile benign melanoma).
Minerva Dermatol 1965;40:463-471

Sapuppo A.
On evolution of Spitz nevus.
Minerva Dermatol 1965;40:61-68

Review Article

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We herewith present a study designed to clarify the issues and offer five criteria for histological differentiation of the nevus in point from malignant melanoma.

We also suggest a new name for it and supporting arguments therefor.

(Arch Dermatol 114:1811-1823, 1978)

This is a study of the histological features of 200 specimens of that distinctive melanocytic nevus, which was originally designated juvenile melanoma by Spitz, collected during a three-year period in the Dermatopathology Laboratory of the New York University Medical Center. To us, the term "nevus of large spindle and/or epithelioid cells" is most informative because it describes and emphasizes those microscopic characteristics that differentiate this nevus from all other melanocytic nevi and from malignant melanoma.

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We have classified the nevus of large spindle and/or epithelioid cells by histological patterns and by cell types. By pattern, they were found to be junctional in 9.5% of the cases, compound in 66%, and intradermal in 24.5%. By cell type, they were predominantly spindle-shaped in 34.5% of all cases, predominantly epithelioid in 21%, or a combination of both cell types in 24.5%. Some histological variants were found and described as granulomatous, lichenoid, and desmoplastic. Specimens that were acanthotic and papillomatous with prominent telangiectasias, severe edema of the dermis, and containing "acantholytic" epithelioid cells and scant melanin were identifiable as coming from young children; those that were dome-shaped and associated with isolated large spindle and/or epithelioid cells in a markedly fibrotic dermis were considered to be from adults.

An attempt has been made to establish histological criteria for the recognition of every pattern and type of nevus of large spindle and/or epithelioid cells and for differentiating them from malignant melanomas. These criteria have been categorized, according to importance, as major and minor features. The major features of nevus of large spindle and/or epithelioid cells are some unusually large cells, spindle and/or epithelioid cells, sharp lateral demarcation of the intraepidermal melanocytic component of the lesion (no horizontal extension of individual melanocytes), rare or sparse individual melanocytes high above the epidermal basal layer, and progressive maturation of nevus cells the deeper they lie in the dermis. Minor features, those that are found commonly enough but are not crucial for diagnosis, are telangiectasia, perivascular inflammatory cell infiltrates, epidermal hyperplasia, clefts between nests of melanocytes and surrounding epidermal keratinocytes, giant nevus cells, fibrosis, edema, and scanty melanin.

Finally, the most important reports about this nevus have been critically reviewed and differences of opinion have been brought into sharper focus.

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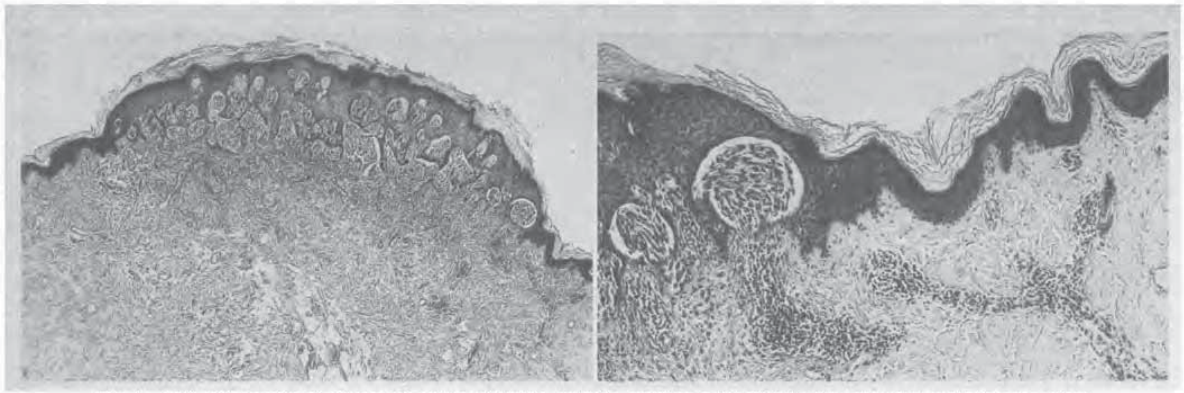

Fig 1.—Left, Diagnostic features of nevus of large spindle and/or epithelioid cells showing well-circumscribed melanocytic lesion in epidermis (ie, intraepidermal melanocytic component stops abruptly in horizontal dimension), elongated nests of epidermal melanocytes oriented perpendicular to surface of specimen, clefts between nests of epidermal melanocytes and surrounding keratinocytes, epidermal hyperplasia, hypergranulosis and hyperkeratosis (hematoxylin-eosin, original magnification ×36). Right, Higher power view of Fig 1, left, showing sharp circumscription of lateral aspect of intraepidermal melanocytic component. Note that there is no horizontal extension of atypical melanocytes, either singly or in small nests, beyond more peripheral nest pictured here (hematoxylin-eosin, original magnification ×40).

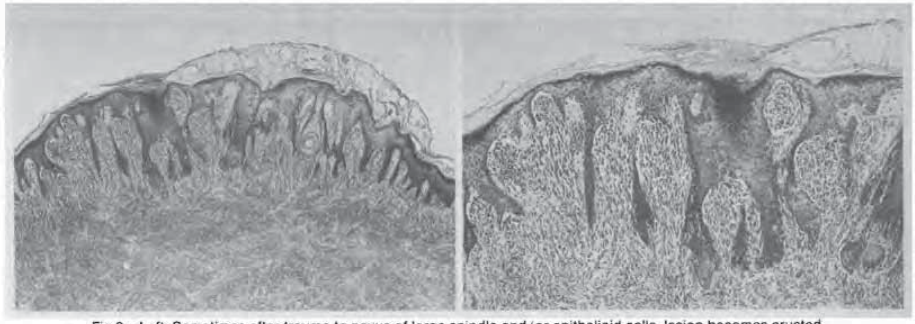

Fig 2.—Left, Sometimes after trauma to nevus of large spindle and/or epithelioid cells, lesion becomes crusted and epidermal hyperplasia is accentuated, as shown here (hematoxylin-eosin, original magnification ×34). Right, Higher power view of Fig 2, left, showing scale crust, irregular epidermal hyperplasia, and nests of spindle-shaped melanocytes within epidermis and dermis. Some of melanocytes are multinucleated (hematoxylin-eosin, original magnification ×80).

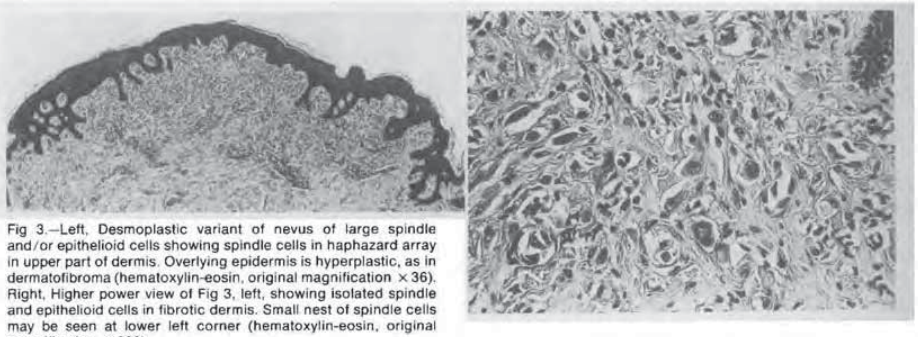

Fig 3.—Left, Desmoplastic variant of nevus of large spindle and/or epithelioid cells showing spindle cells in haphazard array in upper part of dermis. Overlying epidermis is hyperplastic, as in dermatofibroma (hematoxylin-eosin, original magnification ×36). Right, Higher power view of Fig 3, left, showing isolated spindle and epithelioid cells in fibrotic dermis. Small nest of spindle cells may be seen at lower left corner (hematoxylin-eosin, original magnification ×300).

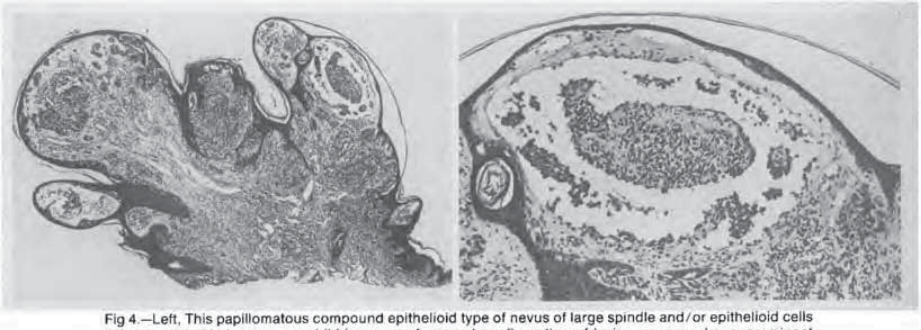

Fig 4.—Left, This papillomatous compound epithelioid type of nevus of large spindle and/or epithelioid cells is unquestionably from young child because of general configuration of lesion, severe edema, prominent vasculature, and tendency of cuboidal nevus cells to separate one from another (hematoxylin-eosin, original magnification ×9). Right, "Acantholytic" cuboidal nevus cells, edematous stroma, and increased number of dilated vessels are all signs of nevus of large spindle and/or epithelioid cells in youngster (hematoxylin-eosin, original magnification ×36).

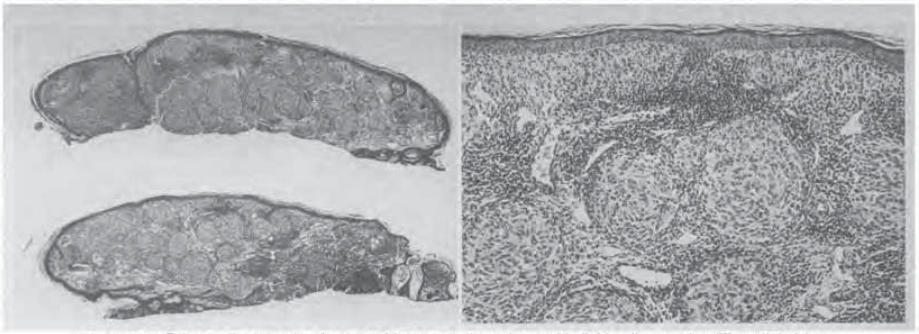

Fig 5.—Left, This sessile example of nevus of large spindle and/or epithelioid cells must be differentiated from granulomatous dermatitis. However, granulomatous processes are practically never sessile and their epithelioid cells are histiocytic rather than melanocytic (hematoxylin-eosin, original magnification ×9). Right, Higher power view of Fig 5, left, showing epithelioid melanocytes that simulate epithelioid histiocytes (hematoxylin-eosin, original magnification ×40).

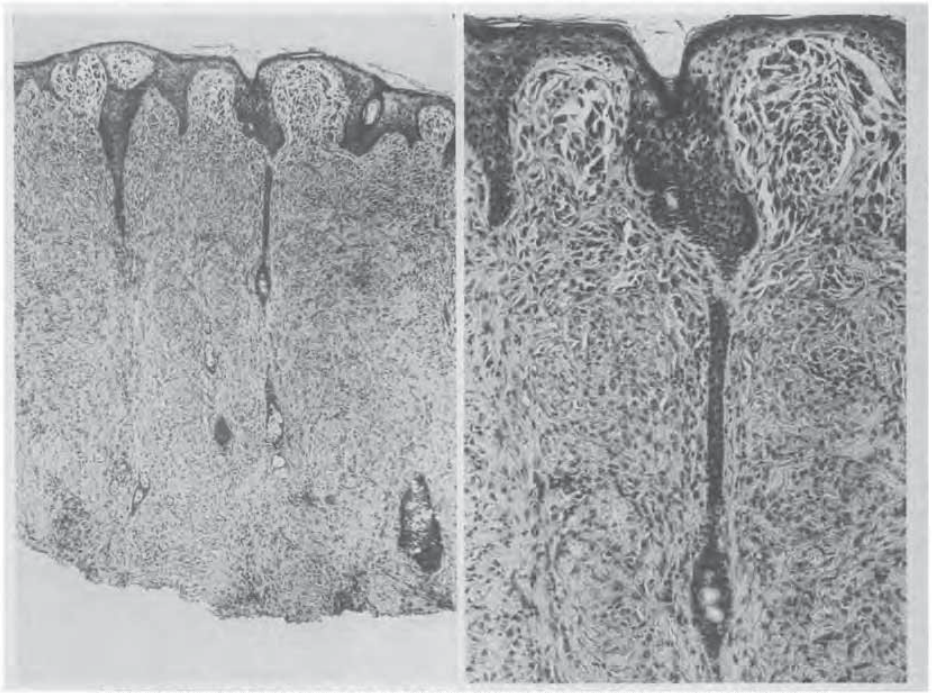

Fig 6.—Left, Fibrosis is often feature of nevus of large spindle and/or epithelioid cells, as illustrated here. In addition to fibrosis, lesion shows numerous multinucleated nevus cells in upper part of dermis and maturation of nevus cells in lower part (hematoxylin-eosin, original magnification ×36). Right, Multinucleated giant nevus cells and fibrosis are better seen in this higher power view of Fig 6, left (hematoxylin-eosin, original magnification ×90).

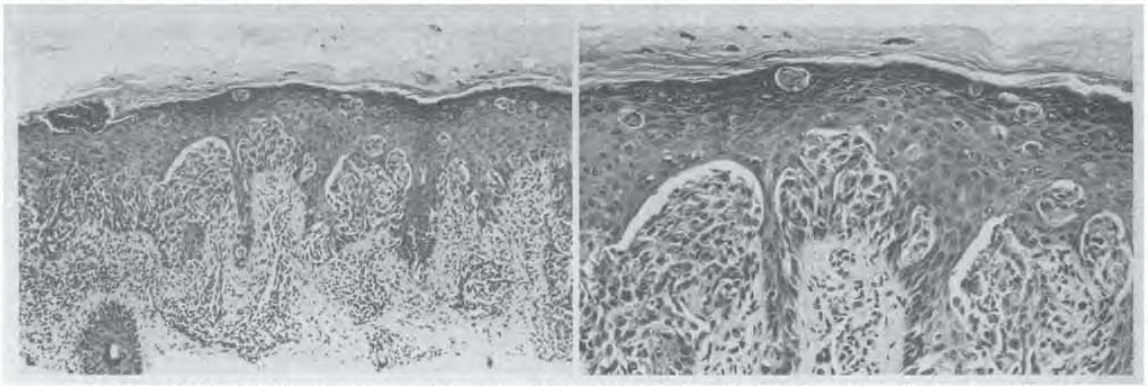

Fig 7.—Left and right, Melanocytes in nevus of large spindle and/or epithelioid cells are usually confined to lower half of epidermis but, episodically, some melanocytes may be found (both singly and in nests) at all levels of epidermis, including cornified layer, as shown here. This is Spitz's nevus, rather than malignant melanoma, because of elongated nests of melanocytes, clefts, irregular epidermal hyperplasia, hypergranulosis, and hyperkeratosis. Furthermore, although not pictured here, intraepidermal melanocytic component was sharply circumscribed laterally (left, hematoxylin-eosin, original magnification ×36; right, hematoxylin-eosin, original magnification ×90).

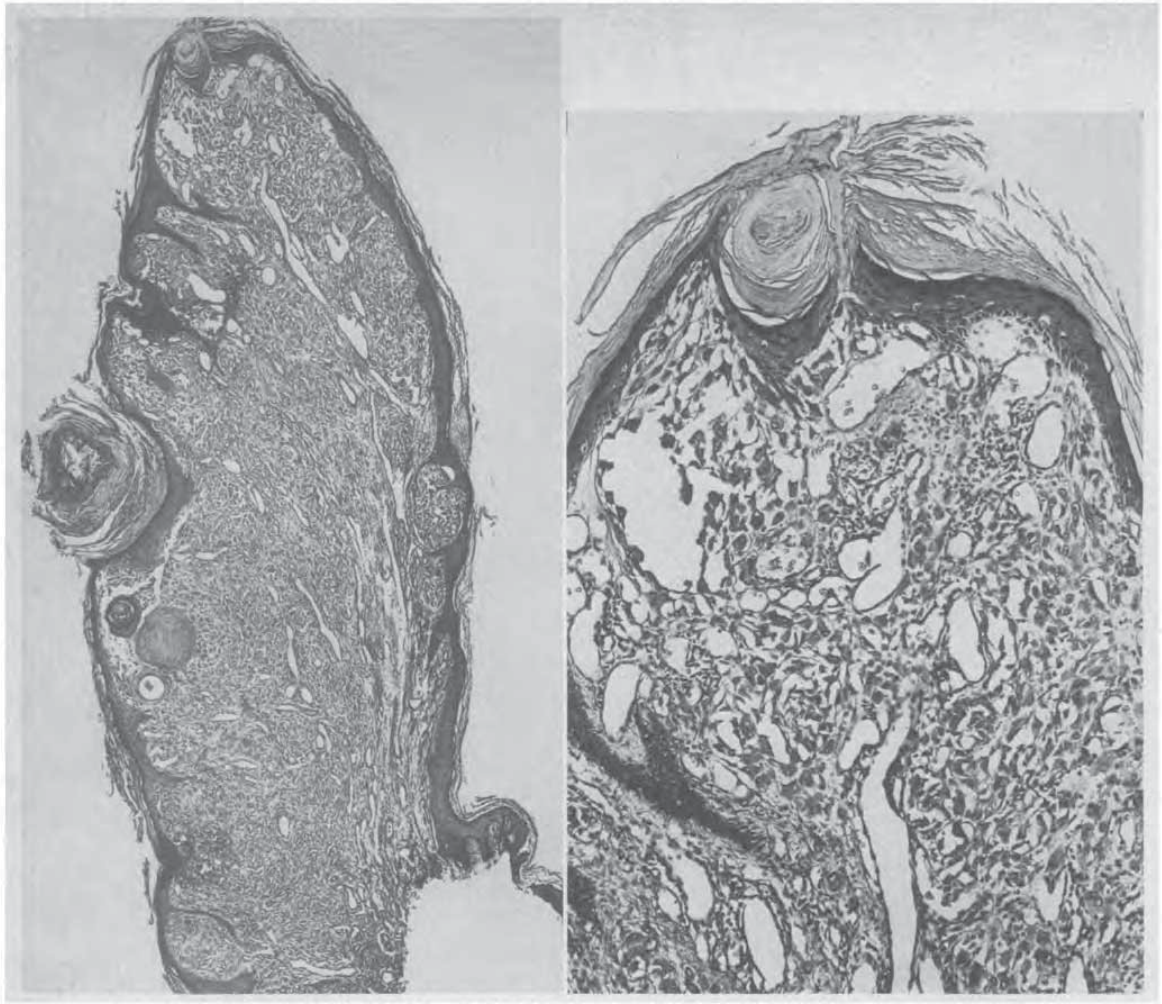

Fig 8.—Left and right, Pink color of some large spindle and/or epithelioid cell nevi in children results, in large part, from widely dilated blood vessels and relative absence of melanin, as pictured here. This is compound epithelioid type of Spitz's nevus (left, hematoxylin-eosin, ×9; right, hematoxylin-eosin, original magnification ×36).

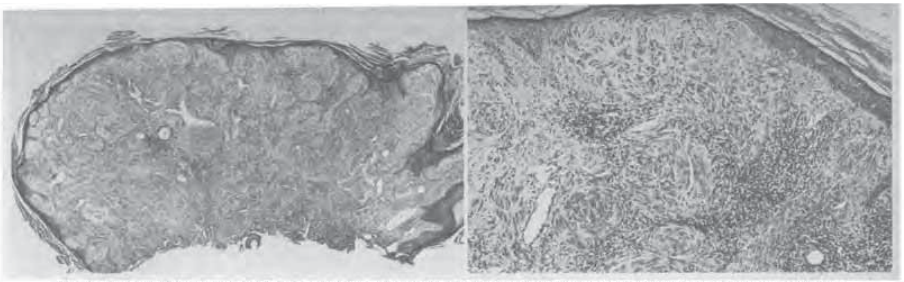

Fig 9.—Left and right, In nevus of large spindle and/or epithelioid cells shown here, predominantly lymphocytic infiltrate is present around vessels throughout lesion, whereas in malignant melanomas, infiltrate is usually present beneath neoplasm (left, hematoxylin-eosin, original magnification ×9; right, hematoxylin-eosin, original magnification ×36).

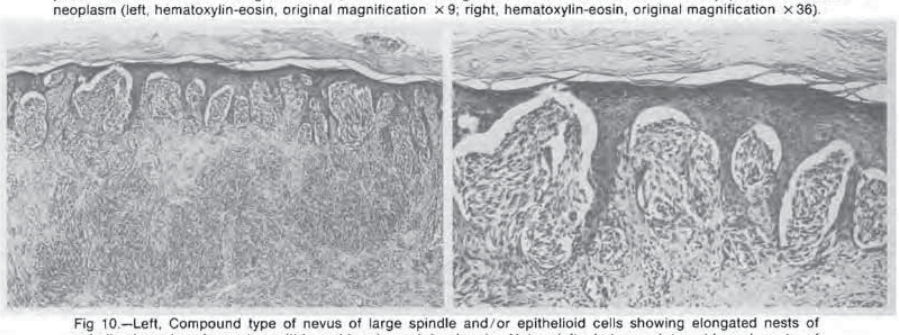

Fig 10.—Left, Compound type of nevus of large spindle and/or epithelioid cells showing elongated nests of spindle-shaped melanocytes within epidermis and in dermis. Note clefts between intraepidermal nests of melanocytes and surrounding keratinocytes, irregular epidermal hyperplasia, hypergranulosis, and hyperkeratosis (hematoxylin-eosin, original magnification ×30). Right, Higher power view of Fig 10, left, showing to better advantage elongated nests of melanocytes, clefts, epidermal hyperplasia, hypergranulosis, and hyperkeratosis (hematoxylin-eosin, original magnification ×90).

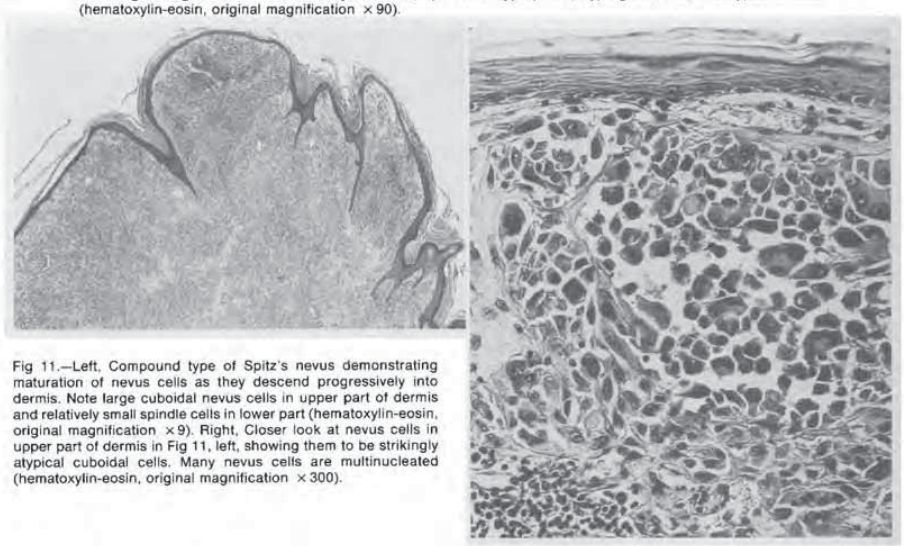

Fig 11.—Left, Compound type of Spitz's nevus demonstrating maturation of nevus cells as they descend progressively into dermis. Note large cuboidal nevus cells in upper part of dermis and relatively small spindle cells in lower part (hematoxylin-eosin, original magnification ×9). Right, Closer look at nevus cells in upper part of dermis in Fig 11, left, showing them to be strikingly atypical cuboidal cells. Many nevus cells are multinucleated (hematoxylin-eosin, original magnification ×300).

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Major features

Large melanocytic cells

Spindle and/or epithelioid cells

Sharp lateral demarcation of the nests of intraepidermal melanocytes

Maturity of cells (i.e., the melanocytes become smaller with progressive descent in the dermis)

Rarity of individual melanocytes high above the basal cell layer

Minor features

Teleangectasia of the upper dermal vessels

Inflammatory infiltrate

Epidermal hyperplasia

Clefts separating nests of melanocytes from the surrounding keratinocytes

Giant melanocytes

Dermal fibrosis

Edematous appearance of the papillary dermis

Sparsity or complete lack of pigmentation

Mitoses (usually not more than 2 per high power field)

The American Journal of Dermatopathology
Volume 1 Number 4
Winter 1979

Findings by Conventional Microscopy:

Hideko Kamino, M.D.

Elissa Misheloff, B.A.

A. Bernard Ackerman, M.D.

Findings by Electron Microscopy:

Thomas J. Flotte, M.D.

M. Alba Greco, M.D.

Eosinophilic globules in Spitz's nevi

New findings and a diagnostic sign

ABSTRACT Dull pink globules were found within the epidermis in 65% of junctional, 75% of compound, and 25% of intradermal types of Spitz's nevi (the nevi of large spindle and/or epithelioid cells). These globules were PAS-positive, diastase-resistant and also were positive with the trichrome stain. Similar-appearing eosinophilic globules were noted in the epidermis in only 2% of malignant melanomas and in but 0.9% of ordinary melanocytic nevi. The globules in malignant melanomas and in ordinary melanocytic nevi were negative with PAS and trichrome stains. Therefore, the finding of PAS- and trichrome-positive eosinophilic globules within the epidermis is a helpful sign for histologic differentiation of Spitz's nevus from malignant melanoma.

From the Departments of Dermatology and Pathology, New York University School of Medicine, New York, New York.
Current address: Centro Médico La Raza, Instituto Mexicano del Seguro Social, Mexico City (HK); fourth-year medical student, New York Medical College (EM).

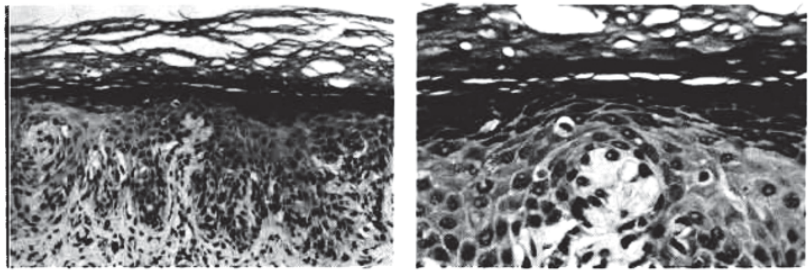
The histologic differentiation of Spitz's nevus (the nevus of large spindle and/or epithelioid cells) from malignant melanoma is of utmost importance in dermatopathology. Most authors agree that no single histologic finding enables absolute differentiation of the benign neoplasm from the malignant one. One of us (HK), while reviewing a large series of melanocytic lesions, observed distinctive eosinophilic globules within the epidermis and the dermis of many specimens of Spitz's nevus. The microscopic appearance of these globules and their significance is the subject of this paper.

MATERIALS AND METHODS

Two hundred ninety-three examples of Spitz's nevi that were junctional, compound, or intradermal were studied in sections stained by hematoxylin and eosin. In addition, as controls, equal numbers of malignant melanomas of all types and of melanocytic nevi that were junctional, compound, or intradermal were also studied. Some sections that showed eosinophilic globules were stained by PAS and by PAS after digestion with diastase, crystal violet, and trichrome.

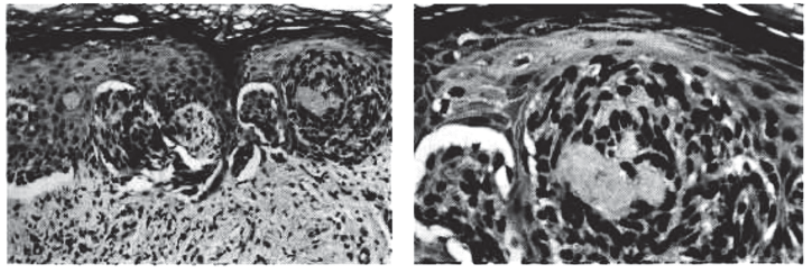
Histologic findings

Eosinophilic globules, singly (10 μ) and in aggregates (110 μ), were found in the epidermis of 175 of



(a) (b)

FIGURES 1a and 1b
In the epidermis above the tip of a dermal papilla in the center of the field are small, dull pink homogeneous globules in a small round aggregate. Note the single more brightly eosinophilic dyskeratotic cell at the left of the aggregate of dull pink globules.



(a) (b)

FIGURES 2a and 2b
In this typical Spitz's nevus, dull pink homogeneous globules may be seen within the center of nests of melanocytes within the epidermis and seemingly within the keratinocytic portion of the epidermis. The higher magnification shows an aggregate of eosinophilic globules within a nest of melanocytes.

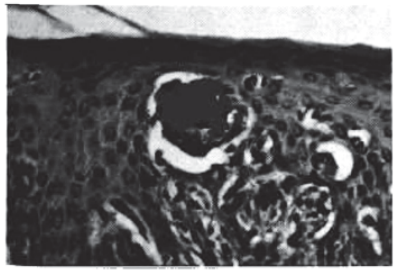


FIGURE 3
The eosinophilic globules in Spitz's nevus take the PAS stain as shown here. The globules are resistant to diastase.

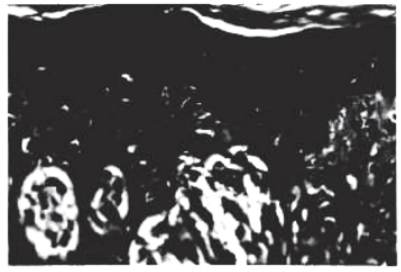
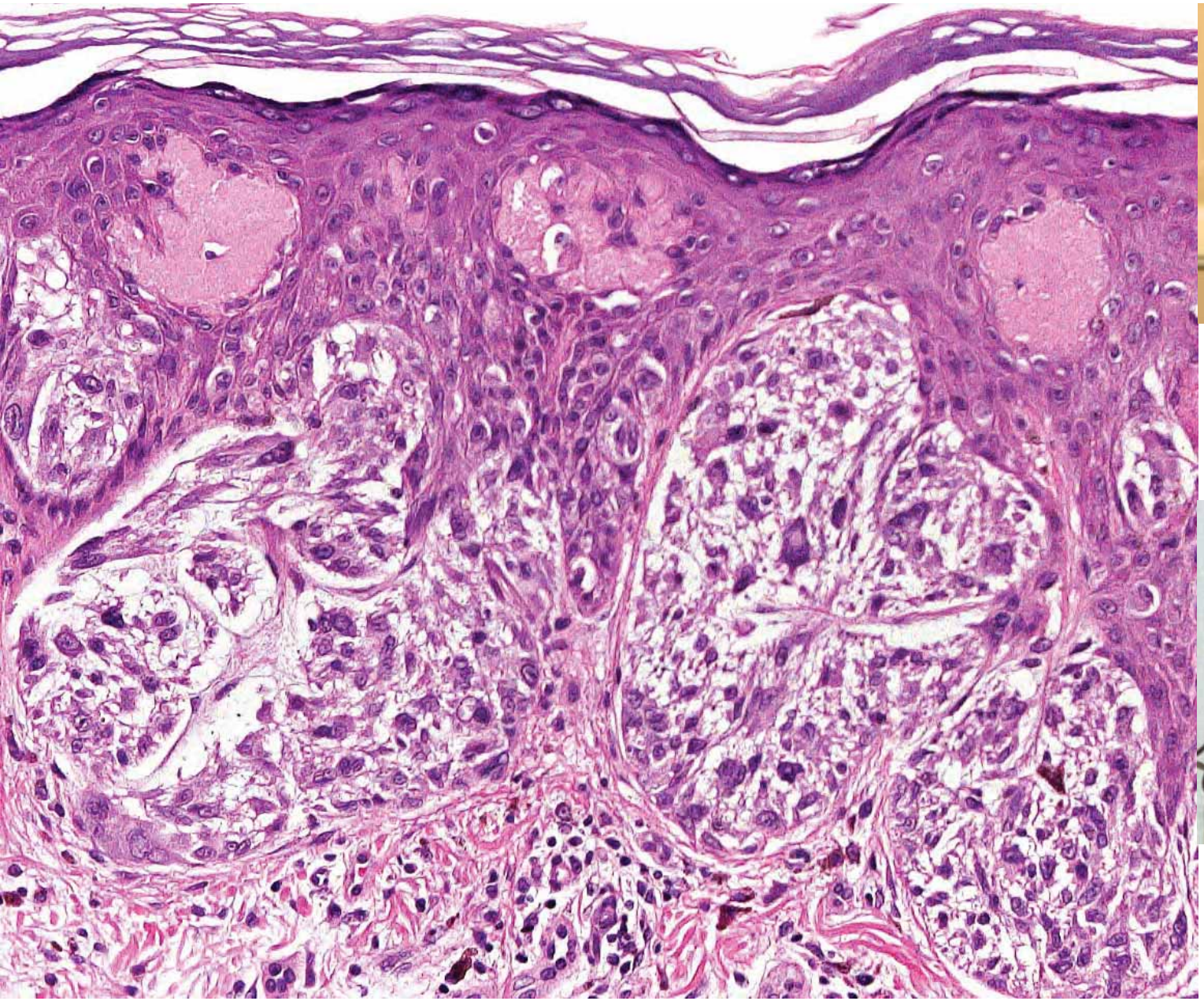


FIGURE 4
The eosinophilic globules in the lower part of the epidermis are colored blue with the trichrome stain, as seen in the photomicrograph.



Whole dermatopathological community:

Kamino bodies

A.B. Ackerman:

Dull pink globules

The American Journal of Surgical Pathology 13(11): 931–939, 1989

Spindle Cell and Epithelioid Cell Nevi with Atypia and Metastasis (Malignant Spitz Nevus)

Kathleen J. Smith, LTC MC USA, Terry L. Barrett, CDR MC USN, Henry G. Skelton III, CDR MC USN, George P. Lupton, COL MC USA, and James H. Graham, M.D.

We report on the clinical and pathologic features of 32 lesions diagnosed as malignant spindle cell and epithelioid cell nevus (S&E nevus). Because of the clinical or initial histopathologic diagnosis of malignant melanoma, six patients had lymph node dissection. Three of these patients also had an enlarged lymph node. In all six cases, metastatic spindle or epithelioid cells were found in at least one of the resected lymph nodes. Of the 30 patients with follow-up information, including all six patients with lymph node metastases, all are alive and well. No recurrences or further metastases have been found. On histopathologic reevaluation, all the lesions had features of S&E nevi. Study of these cases suggests that although some lesions with features of S&E nevi may involve local lymph nodes, widespread metastases do not result.

Key Words: Spindle cell and epithelioid cell nevus—Nevi with metastasis—Spitz nevus—Skin.

Am J Surg Pathol 13(11): 931–939, 1989.

The histologic criteria for the diagnosis of spindle cell and epithelioid cell nevus (S&E nevus) were first described in 1948 by Dr. Sophie Spitz (25). Prior to Dr. Spitz's publication, S&E nevi were considered to be histologically indistinguishable from malignant melanomas (MM) of adults (19); they were called "juvenile melanomas." Because they were (thought) to be highly susceptible to malignant transformation, the treatment of choice was surgical removal prior to puberty (19). However, Pack and Angelem stated in 1939 that these juvenile melanomas seldom metastasize (19) and lethal MM in children are very rare.

In 1954, McWhorter and Woolner reviewed the material at the Mayo Clinic and confirmed the opinion of Spitz that "juvenile melanomas" are clinically benign lesions (19). In 1954, Helwig argued that the term "juvenile melanoma" was inappropriate because these lesions also occur in adults and because the term "melanoma" has a malignant connotation (12). He proposed the term "spindle cell nevus" because of the lesion's many elongated spindle-shaped cells. In 1960, Kernen and Ackerman introduced the term "spindle cell and epithelioid cell nevus" (12).

In 1953, Allen and Spitz established the following criteria for differentiating S&E nevus from MM (18): (a) features of a compound nevus, (b) edema and telangiectasia in the upper portion of the dermis, (c) nests of cells sharply separated from the surrounding keratinocytes, (d) large spindle or epithelioid cells, (e) Touton-like giant cells, (f) abrupt transition between acantholytic cells in the junctional nests and the intact adjacent epidermis; (g) relative sparsity of pigmentation, and (h) relative superficiality of the major landmarks of the lesion. At the Armed Forces Institute of Pathology (AFIP), we have seen uncommon lesions that in addition to

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The opinions or assertions contained herein are the private views of the authors and are not to be considered as official or as reflecting the views of the Department of the Army, the Department of the Navy, or the Department of Defense.

3/32 cases with palpable lymph nodes.

Another 3 in which lymph node involvement was detected on elective dissection.

30/30 patients with follow-up data are alive and well

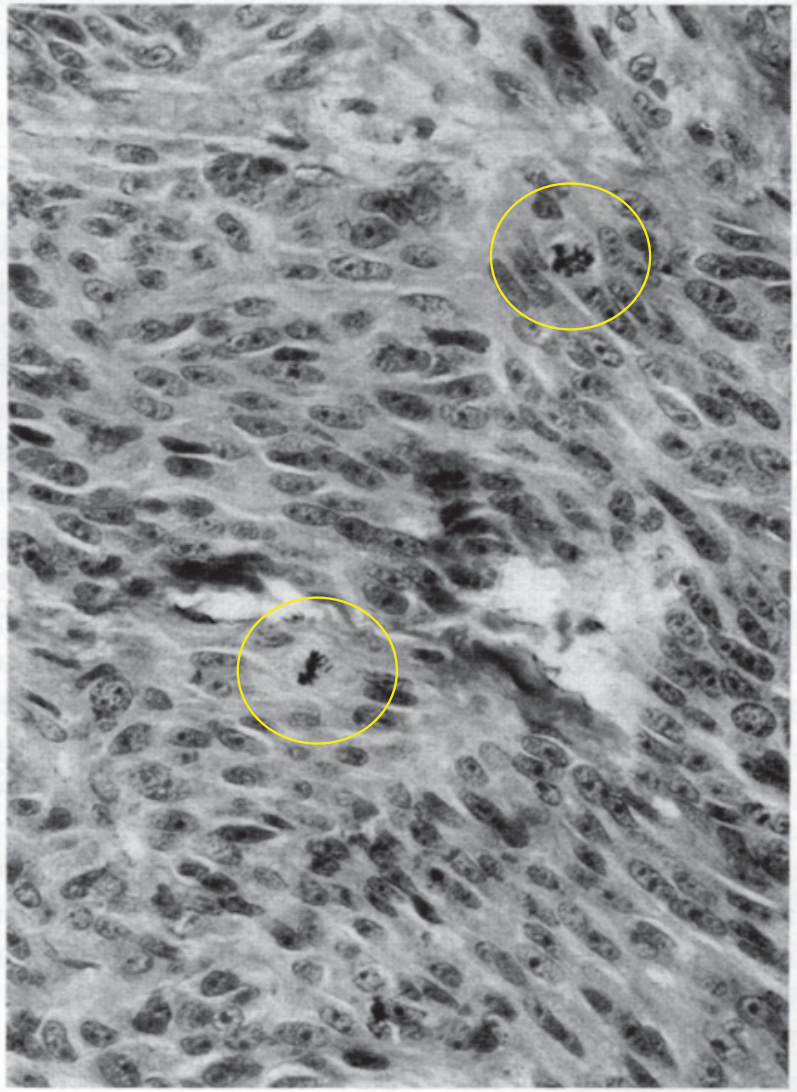


FIG. 7. Mitotic figures may be present deep in the nevus.

(a)

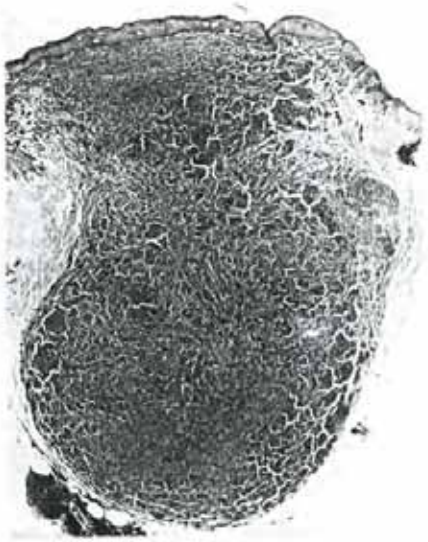
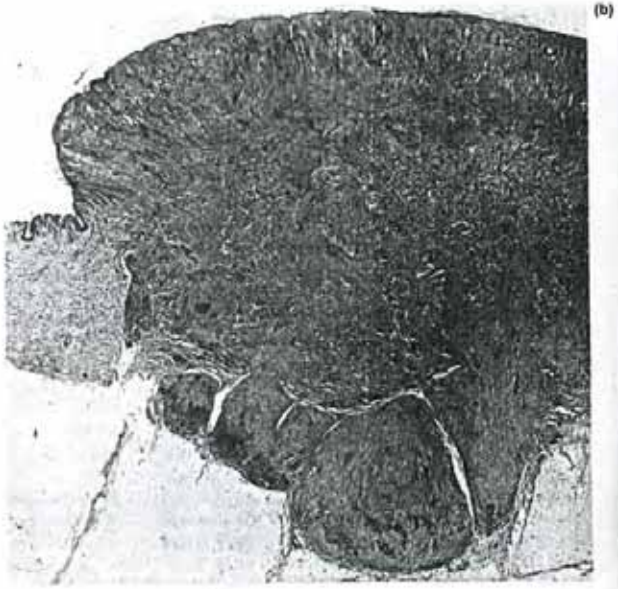


FIG. 1. Three examples of lesions that extend deep into the subcutaneous fat (Fig. 1c on facing page).

(b)



(c)

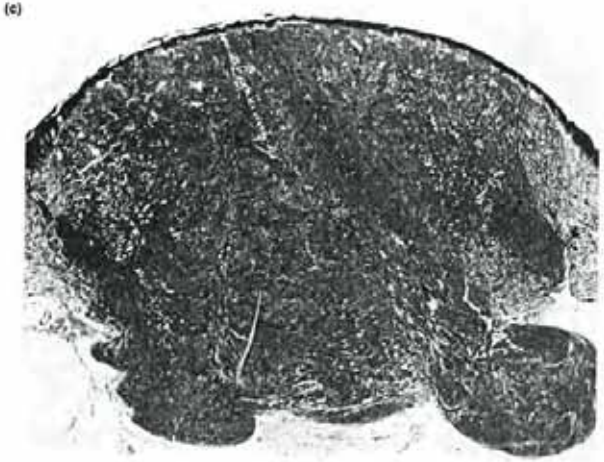
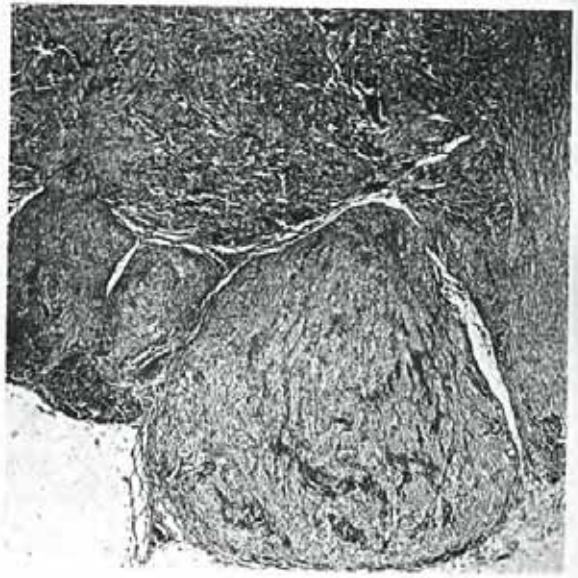


FIG. 2. Higher-power view of Fig. 1b. The deep margin is rounded and pushing rather than infiltrating. This lesion also illustrates the lymphoid infiltrate around the lesion as well as perivascularly. The infiltrate contains numerous plasma cells.



Atypical Spitz Nevi/Tumors: Lack of Consensus for Diagnosis, Discrimination From Melanoma, and Prediction of Outcome

RAYMOND L. BARNHILL, MD, ZSOLT B. ARGENYI, MD, LYNN FROM, MD, L. FRANK GLASS, MD, JOHN C. MAIZE, MD, MARTIN C. MIHM, JR., MD, MICHAEL S. RABKIN, MD, PHD, SALVE G. RONAN, MD, WAIN L. WHITE, MD, AND MICHAEL PIEPKORN, MD, PHD

The biological nature of Spitz nevi/tumors and their diagnostic distinction from, or relationship to, melanoma remain unresolved issues. In this report, a series of 30 melanocytic lesions removed from 28 patients, including atypical Spitz nevi/tumors and metastasizing Spitzoid tumors/melanomas, were evaluated by a panel of dermatopathologists to evaluate interobserver diagnostic concordance and to assess the prognostic power of histological criteria. For inclusion in the study, each lesion had to display some criteria for the Spitz nevus, and in addition one of the following was required: (1) definitive clinical outcome such as metastasis or death of disease, or (2) long-term follow-up if the patient remained disease free. Each lesion was reviewed independently and blinded as to the clinical data by 10 pathologists, who categorized them as (1) typical Spitz nevus/tumor, (2) atypical Spitz nevus/tumor, (3) melanoma, (4) tumor with unknown biological potential, or (5) other melanocytic lesion. There was limited discussion of criteria before the review. Evaluation of 17 Spitzoid lesions yielded no clear consensus as to diagnosis; in only one case did six or more pathologists agree on a single category, regardless of clinical outcome. Notably, however, some lesions that proved fatal were categorized by most observers as either Spitz nevi or atypical Spitz tumors. Conversely, seven or more pathologists scored 13 lesions as melanoma. These results illustrate (1) substantial diagnostic difficulties posed by many Spitz tumors, especially those with atypical features, even among experts, and (2) the lack of objective criteria for their distinction from melanoma and for gauging their malignant potential. Nevertheless, our observations do suggest that a biological relationship exists between the Spitz nevus/tumor and melanoma. HUM PATHOL 30:513-520. Copyright © 1999 by W.B. Saunders Company

Key words: Spitz nevus, Spitz tumors, melanoma, interobserver concordance, prognosis.

One of the more contentious issues in dermatopathology concerns the biological relationship, if any, between melanoma and the Spitz nevus/tumor. (*Melanoma* and *malignant melanoma* are used synonymously in this report; *Spitz nevus*, *Spitz's nevus*, and *Spitz tumor* are used interchangeably herein.) Although there were antecedent accounts in the literature[1] of what have come to be called Spitz nevi,[2,3] Sophie Spitz is credited with their recognition in children and with the difficulty of their histological distinction from melanoma.[4] This difficulty led to the appellation *benign juvenile melanoma*.[5] Spitz maintained that juvenile and conventional melanomas have more features in common than differences, an observation shared by many later observers.[6-10] In view of the diagnostic difficulties presented by Spitz nevi, numerous histological criteria have been proposed for their discrimination from melanoma.[5,7,8,11-18] A perusal of the literature, however, suggests that many Spitz nevi deviate from an idealized or stereotypical depiction that has been promulgated, presenting in many instances considerable difficulties with the differential diagnosis of melanoma. Complicating matters is the unsettling situation that there is no uniformity of opinion in the authoritative, classical articles with regard to the salient features that enable the reliable discrimination of the Spitz nevus from melanoma (eg, compare diagnostic criteria in Weedon and Little,[5] McWhorter and Wollner,[11] Paniago-Pereira et al,[18] and Kernen and Ackerman[18]; Table 1). Similarly, any given set of published guidelines for separating Spitz nevi from melanomas can only be presumptive, because rigorous studies with sufficient numbers of cases with long-term follow-up are not available (eg, Paniago-Pereira et al[18]) for validation of the discriminative criteria by the natural history of the disease. Moreover, practical experience suggests that these lesions clinically as well as histologically may form a continuous phenotypic spectrum overlapping that of melanoma, and it is possible and even perhaps likely that the biological potential of some Spitz nevi may defy the application of prognostic histological criteria.[6,9,10]

Most published case series of Spitz nevi are virtual tautologies, in that the investigators have collected cases retrospectively from their files, then reviewed the histological findings for the purposes of publication. In doing so, the resulting descriptions are not necessarily those of Spitz nevi per se but rather represent that unique set of criteria the authors had originally used for

From the Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; the Department of Dermatology, University of Iowa, Iowa City, IA; the Department of Pathology, Women's College Hospital, University of Toronto, Toronto, Canada; the Department of Dermatology, University of South Florida, Tampa, FL; the Department of Dermatology, Medical University of South Carolina, Charleston, SC; the Department of Dermatology, Albany Medical College, Albany, NY; the Rabkin Dermatopathology Laboratory, PC, Pittsburgh, PA; the Department of Pathology, University of Illinois, Chicago, IL; the Department of Pathology, Bowman Gray School of Medicine, Winston-Salem, NC; and the Division of Dermatology, University of Washington School of Medicine, Seattle, WA.

Address correspondence and reprint requests to Michael Piepkorn, MD, Division of Dermatology, Box 356524, Seattle, WA 98195-6524.

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30 cases, 10 pathologists

metastatic disease (n=19) (7 DoD, age "child"-17)

majority diagnosed SN	3 cases (15,8%)
SN - MM = 5 - 5	2 cases (5,3%)
unanimity MM	6 cases (31,6%)

no metastatic disease (FU 5-16 years) (n=11)

majority diagnosed MM	8 cases (72,7%)
SN - MM = 5 - 5	1 case (9,1%)
unanimity SN	0

"In many cases, the unequivocal distinction between benignity and malignancy may be in practical terms impossible, because the available definitions and distinguishing criteria between melanoma and atypical Spitz tumors are inadequate."

Atypical Spitz Nevi/Tumors: Lack of Consensus for Diagnosis, Discrimination From Melanoma, and Prediction of Outcome

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Key words: Spitz nevus, Spitz tumors, melanoma, interobserver concordance, prognosis.

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South Carolina, Charleston, SC; the Department of Dermatology, Albany Medical College, Albany, NY; the Rabkin Dermatopathology Laboratory, PC, Pittsburgh, PA; the Department of Pathology, University of Illinois, Chicago, IL; the Department of Pathology, Bowman Gray School of Medicine, Winston-Salem, NC; and the Division of Dermatology, University of Washington School of Medicine, Seattle, WA.

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12-year-old girl

A, B: Primary tumor on the thigh

C: 2nd local recurrence (13 months)

D: regional LN (14 years later);

DoD 8 months later

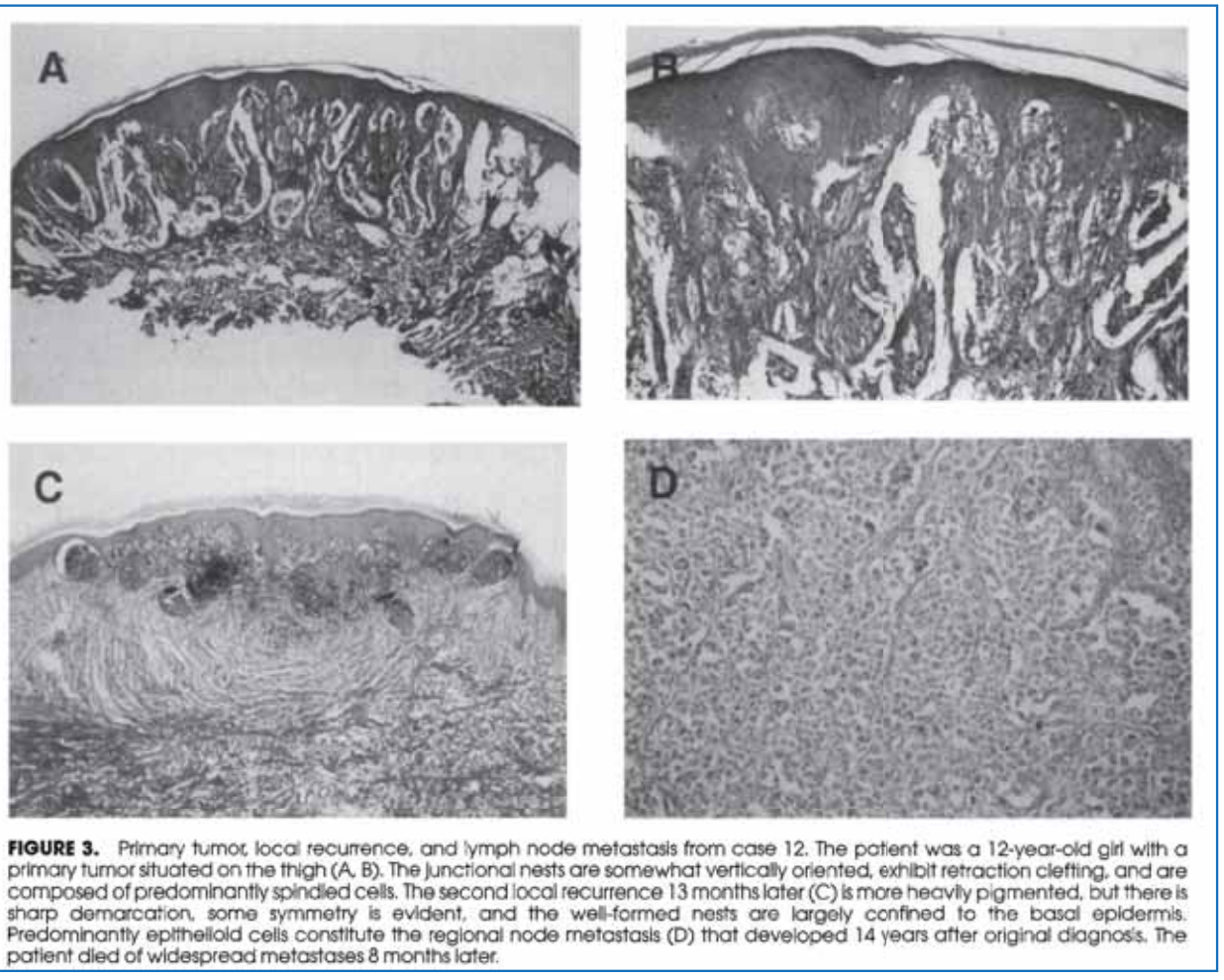
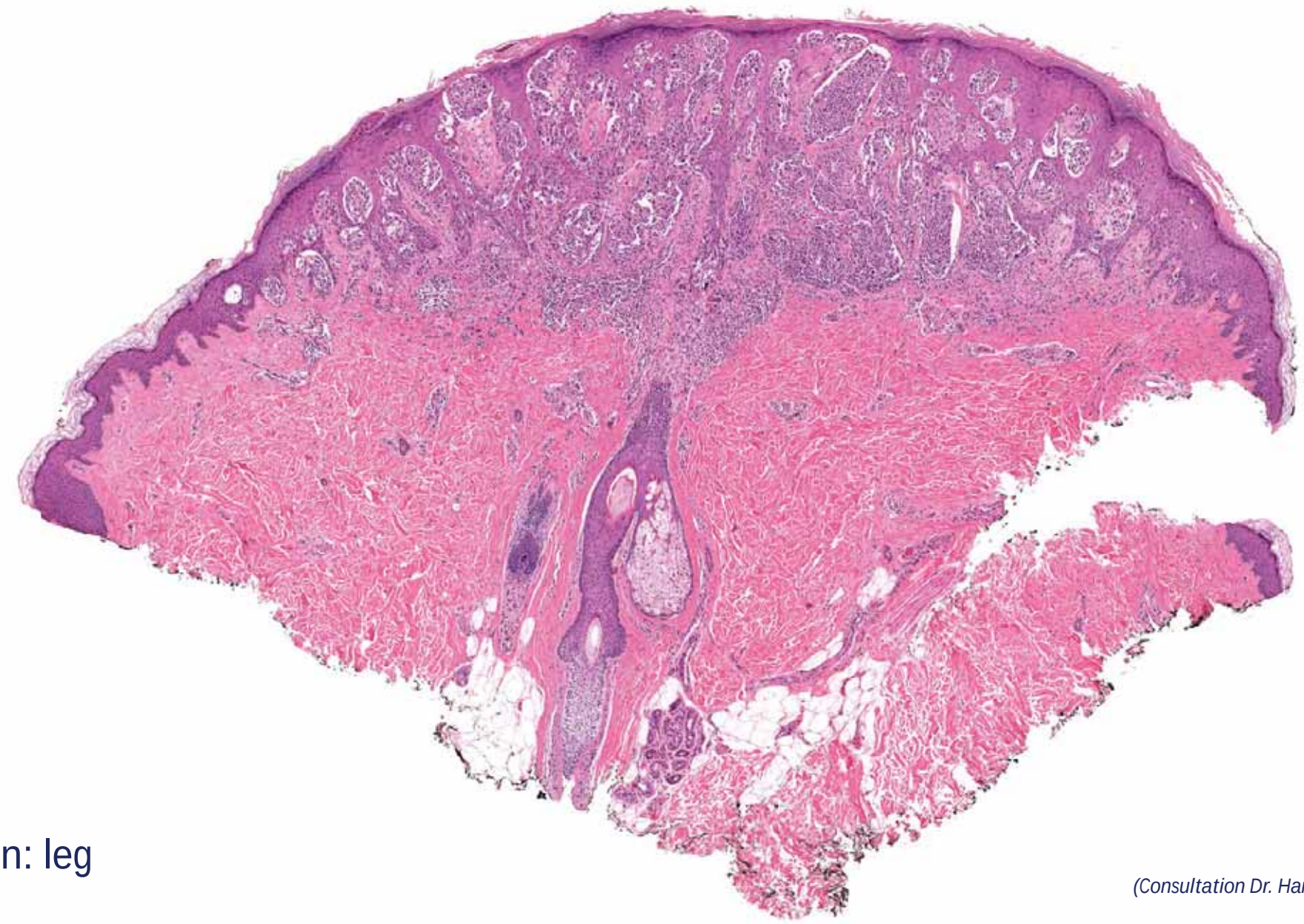


FIGURE 3. Primary tumor, local recurrence, and lymph node metastasis from case 12. The patient was a 12-year-old girl with a primary tumor situated on the thigh (A, B). The junctional nests are somewhat vertically oriented, exhibit retraction clefting, and are composed of predominantly spindled cells. The second local recurrence 13 months later (C) is more heavily pigmented, but there is sharp demarcation, some symmetry is evident, and the well-formed nests are largely confined to the basal epidermis. Predominantly epithelioid cells constitute the regional node metastasis (D) that developed 14 years after original diagnosis. The patient died of widespread metastases 8 months later.

Panelists' diagnoses:

Spitz nevus: 6; Atypical SN: 2; Uncertain biological potential: 2; Melanoma: 0



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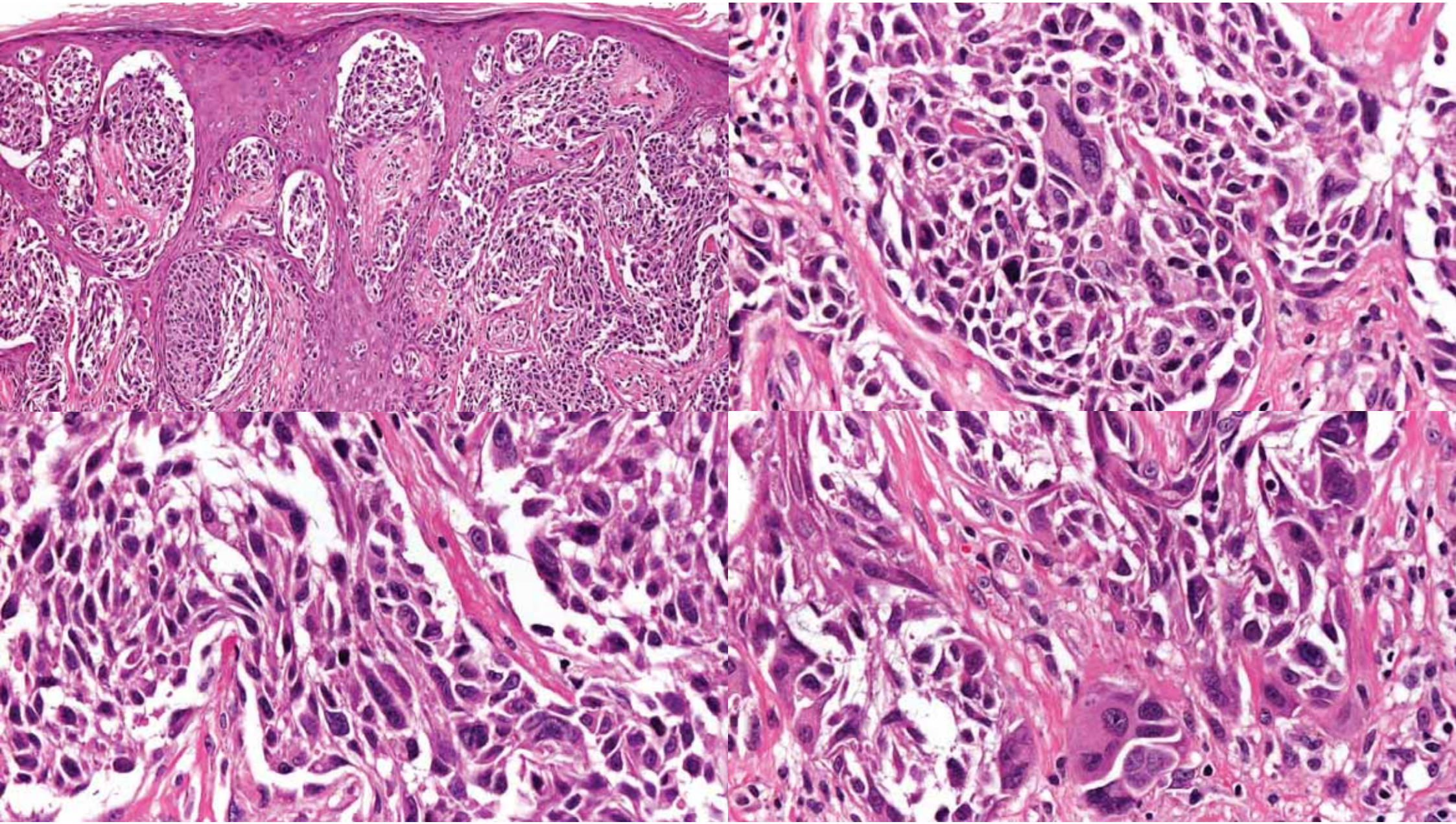
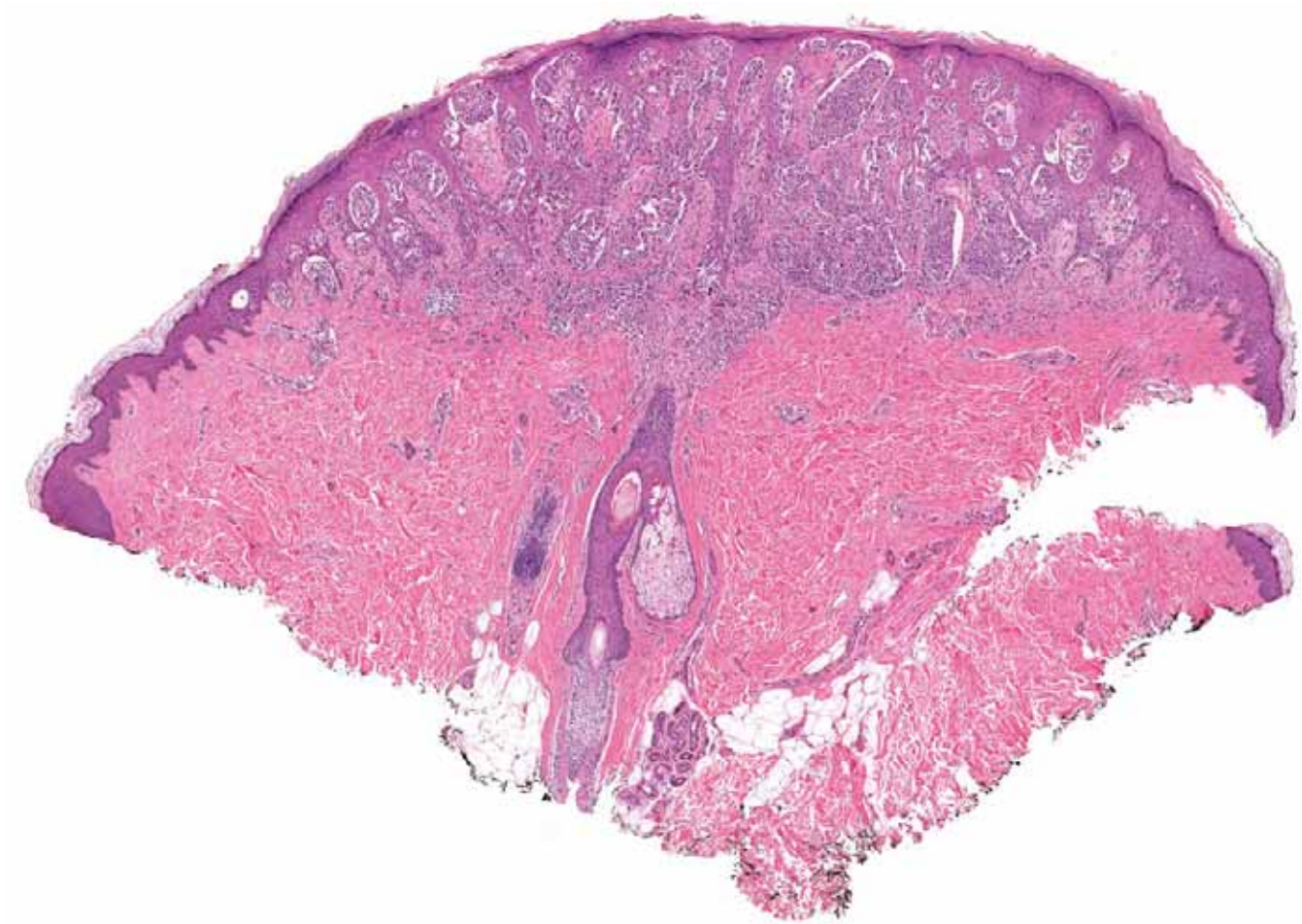
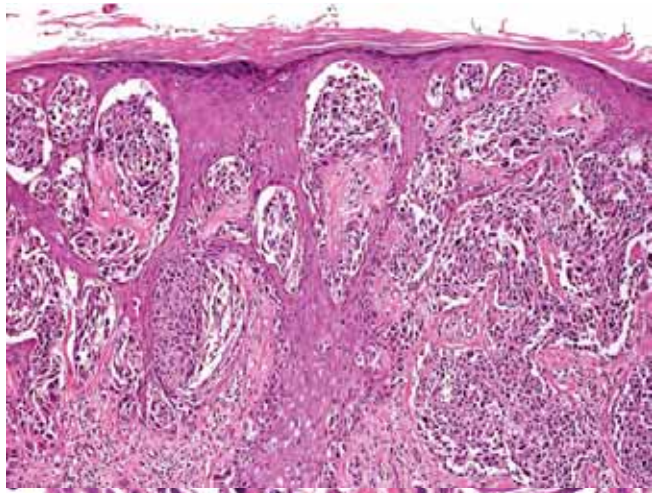
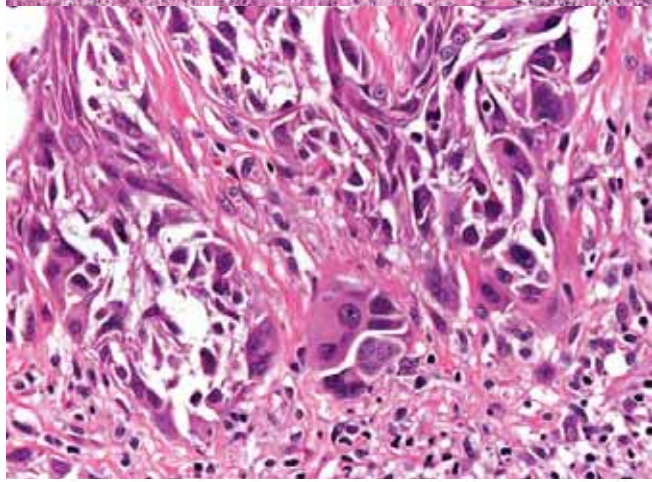
Location: leg

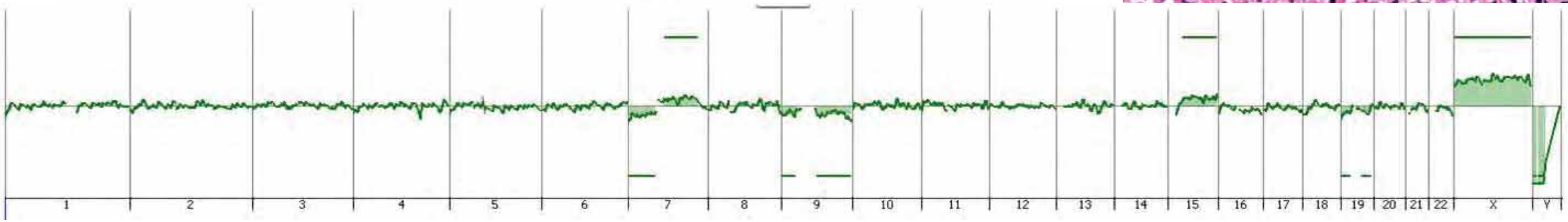
(Consultation Dr. Hansmann, Frankfurt)







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Richard J. Reed
Hum Pathol 30:1523-1525, 1999

CORRESPONDENCE

Atypical Spitz Nevus/Tumor

To the Editor:—In the recent issue of *Human Pathology* dedicated to the memory of Wallace Clark, Barnhill et al[1] reported the results of their study of 30 cases of "atypical Spitz nevus/tumor"; they sought a consensus regarding the nature of each of the 30 lesions. A search for a consensus in pathology is an effort to democratize a position in histological interpreta-

tions. To paraphrase the late Charles E. Dunlap, MD, the practice of pathology is not a democracy; not all opinions are equal.

Barnhill et al[1] noted close aggregation of nests and fascicles of cells in the dermis (ie, patterns of typical vertical growth). Having recorded this observation, they then failed to correlate it with clinical behavior. Patterns of typical vertical growth constitute a prime requisite for the identification of

"(...) the practice of pathology is not a democracy; not all opinions are equal."

Spitz "nevus" should be accepted as a neoplasm with a unpredictable potential for neoplastic progression. The progressions are expressed in uncommon patterns and in varying degrees of cytological atypia. They may be expressed in the qualities of a low-grade melanoma with limited potential for metastasis (usually limited in distribution to regional lymph nodes). Rarely, they are expressed in the qualities of a high-grade melanoma with a potential for widespread dissemination.

"Spitz's nevus":

Reassessment critical, revision radical

A. Bernard Ackerman, M.D.

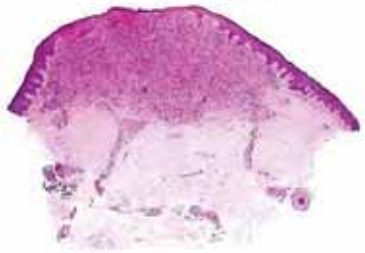
with Diana Elish, M.D. and Samar Shami, M.D.

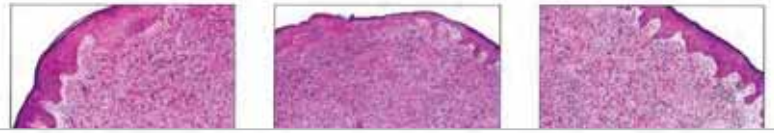
2007

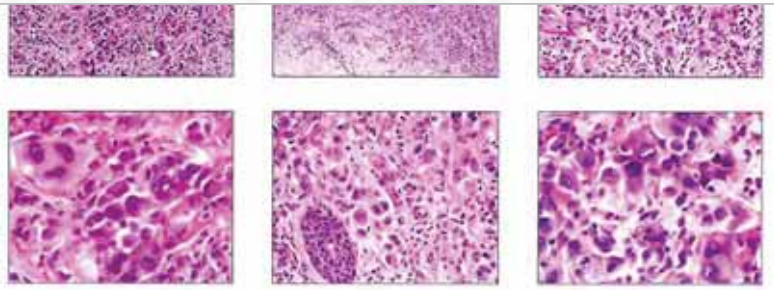
New York, NY
Ardor Scribendi pub.

CASE 15 *What is your diagnosis? Spitz's nevus or spitzoid melanoma?*

7-year-old boy







CASE 15 ANSWER: Spitz's nevus

History: 7-year-old boy

Findings in common:

1. Neoplastic melanocytes extraordinarily large with pleomorphic nuclei and cytoplasm exceedingly copious
2. Shapes of abnormal melanocytes round, oval and polygonal; mononucleate, binucleate and multinucleate giant cells also present
3. Occasional mitotic figure in an abnormal melanocyte
4. Sparse infiltrate of lymphocytes and neutrophils

Findings differentiating:

1.Small neoplasm little more than 3 mm in diameter and nearly 2 mm in depth

3. Although this neoplasm fulfills criteria for Spitz's nevus, a histopathologist cognizant of the snares extraordinary in the matter of interpreting correctly the findings in a lesion such as this one and the reality of fallibility inherent in such interpretation is obligated to communicate in a note to the physician referring a sense of uncertainty, along with an admonition that the lesion MUST be excised *in toto*.

immediately beneath the epidermis. The scatter of neutrophils throughout the neoplasm is a consequence of the surface of it having been ulcerated in the not too distant past.

3. Although this neoplasm fulfills criteria for Spitz's nevus, a histopathologist cognizant of the snares extraordinary in the matter of interpreting correctly the findings in a lesion such as this one and the reality of fallibility inherent in such interpretation is obligated to communicate in a note to the physician referring a sense of uncertainty, along with an admonition that the lesion MUST be excised *in toto*.

Although this neoplasm fulfills criteria for Spitz's nevus, a histopathologist (...) is obligated to communicate to the referring physician a sense of *uncertainty*...

Sophie Spitz (1910-1956)

THE AMERICAN JOURNAL
OF PATHOLOGY

Official Publication of
The American Association of Pathologists and Bacteriologists

VOLUME XXIV

1948

MELANOMAS OF CHILDHOOD *

SOPHIE SPITZ, M.D.

(From the Pathology Laboratories of the Memorial Hospital, New York, N.Y.)

It has become apparent over a period of years that even when a histologic diagnosis of malignant melanoma has been made in children the clinical behavior rarely has been that of a malignant tumor. The disparity in behavior of the melanomas of adults and children, despite the histologic similarity of the lesions occurring in the different age groups, is obviously a matter of fundamental importance and the following questions immediately arise: Does the histologically malignant melanoma of children differ in any structural detail from that of adults? Can the clinical behavior of these lesions be predicted from their histologic structure? What, if any, are the factors known to influence the clinical behavior? Should the melanomas of children be treated any differently from the melanomas of adults?

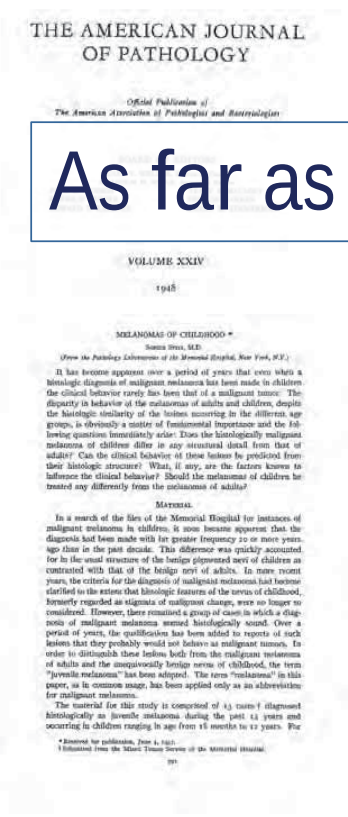
MATERIAL

In a search of the files of the Memorial Hospital for instances of malignant melanoma in children, it soon became apparent that the diagnosis had been made with far greater frequency 20 or more years ago than in the past decade. This difference was quickly accounted for in the usual structure of the benign pigmented nevi of children as contrasted with that of the benign nevi of adults. In more recent years, the criteria for the diagnosis of malignant melanoma had become clarified to the extent that histologic features of the nevus of childhood, formerly regarded as stigmata of malignant change, were no longer so considered. However, there remained a group of cases in which a diagnosis of malignant melanoma seemed histologically sound. Over a period of years, the qualification has been added to reports of such lesions that they probably would not behave as malignant tumors. In order to distinguish these lesions both from the malignant melanoma of adults and the unequivocally benign nevus of childhood, the term "juvenile melanoma" has been adopted. The term "melanoma" in this paper, as in common usage, has been applied only as an abbreviation for malignant melanoma.

The material for this study is comprised of 13 cases † diagnosed histologically as juvenile melanoma during the past 13 years and occurring in children ranging in age from 18 months to 12 years. For

Hospital.

Does a "Spitz nevus" exist ?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VOLUME XXIV

1948

MELANOMAS OF CHILDHOOD *

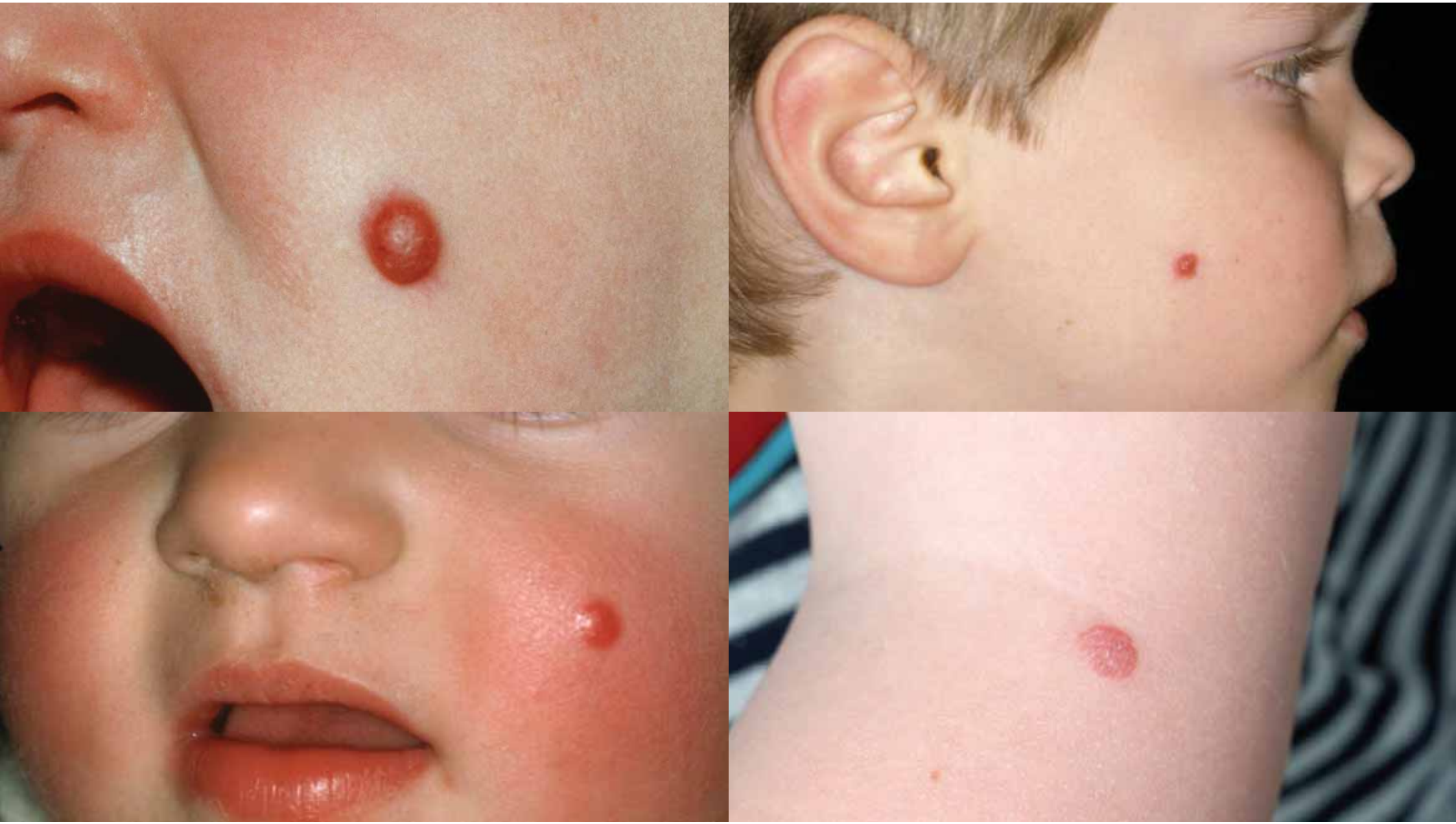
Does a "Spitz nevus" exist ?

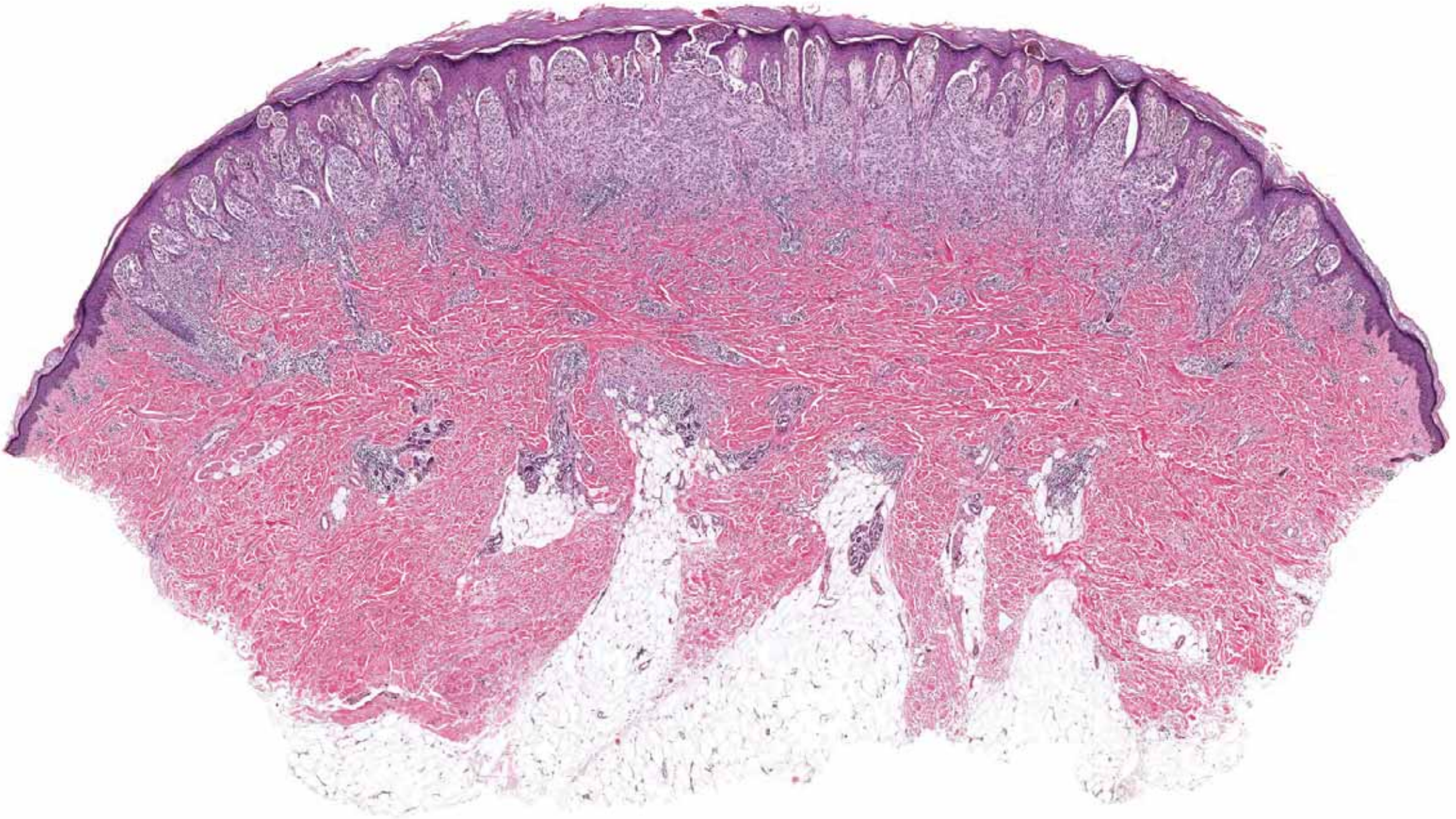
- *One fatal case was characterized by rapid growth of a lesion on the sole of the foot not involving the skin (a soft white tumor, 2 cm. in diameter, was resected from the plantar fascia).* ***My opinion: nothing to do with "Spitz nevi / tumors"***
- 10 lesions under 1 cm. in diameter; 2 between 1 and 3 cm. Gradual increase in size in all 12 cases. 2 lesions were ulcerated.
- 5 lesions pink to red; 7 brown to black.

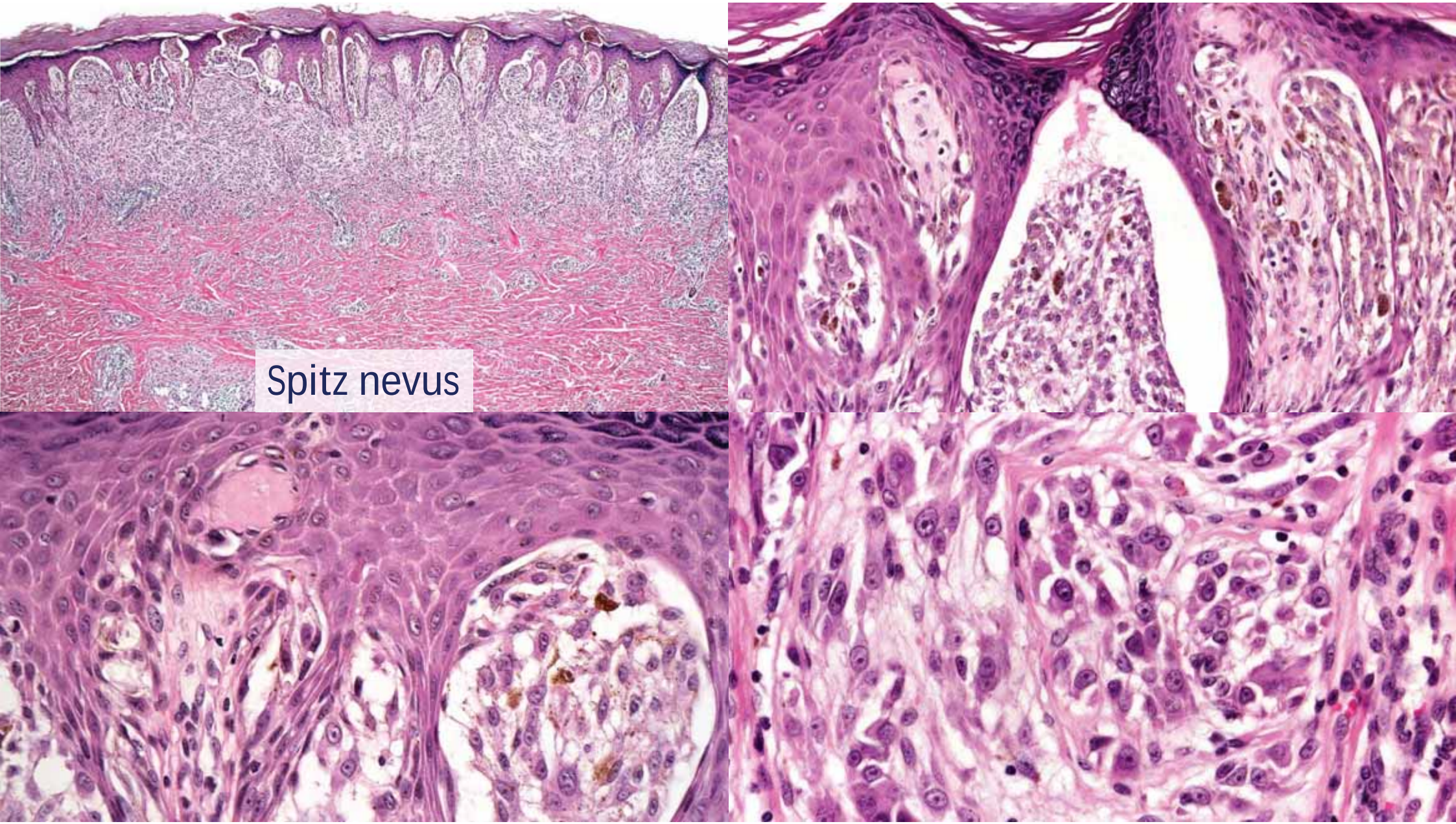
As far as one can judge, a rather heterogenous group of lesions

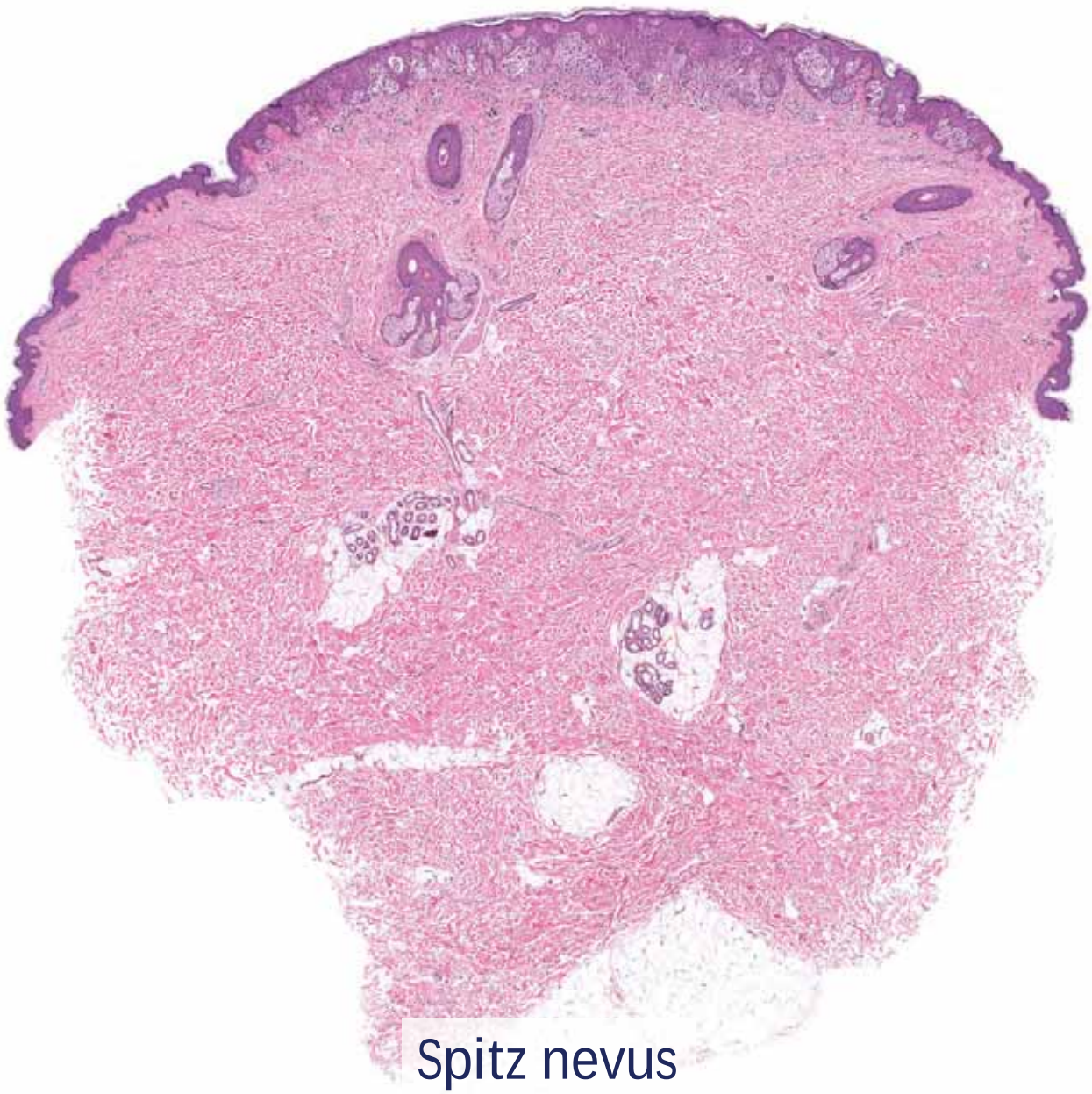
dermis. In 3 cases, the dermal portion of the tumor was composed entirely of spindle cells.

- Pigment was present in all of the lesions but only 3 were heavily pigmented.
- One case was different from the other 11. This lesion had essentially the structure of a simple benign intradermal nevus with clusters and strands of cells extending into the subcutaneous fat. The distinctive feature was the almost uniform enlargement of each cell to a diameter three or four times that of an ordinary nevus cell.

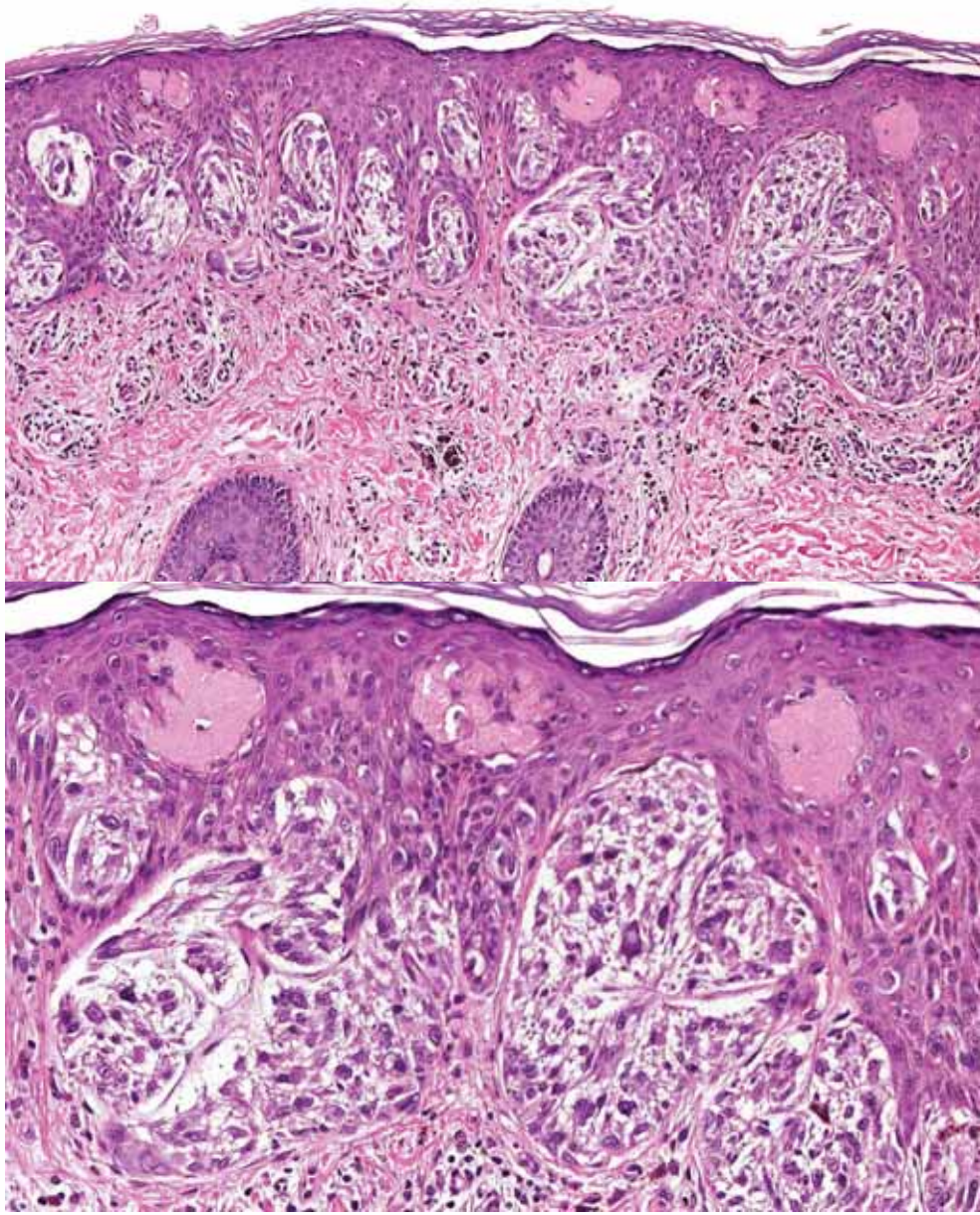





Spitz nevus



Spitz nevus



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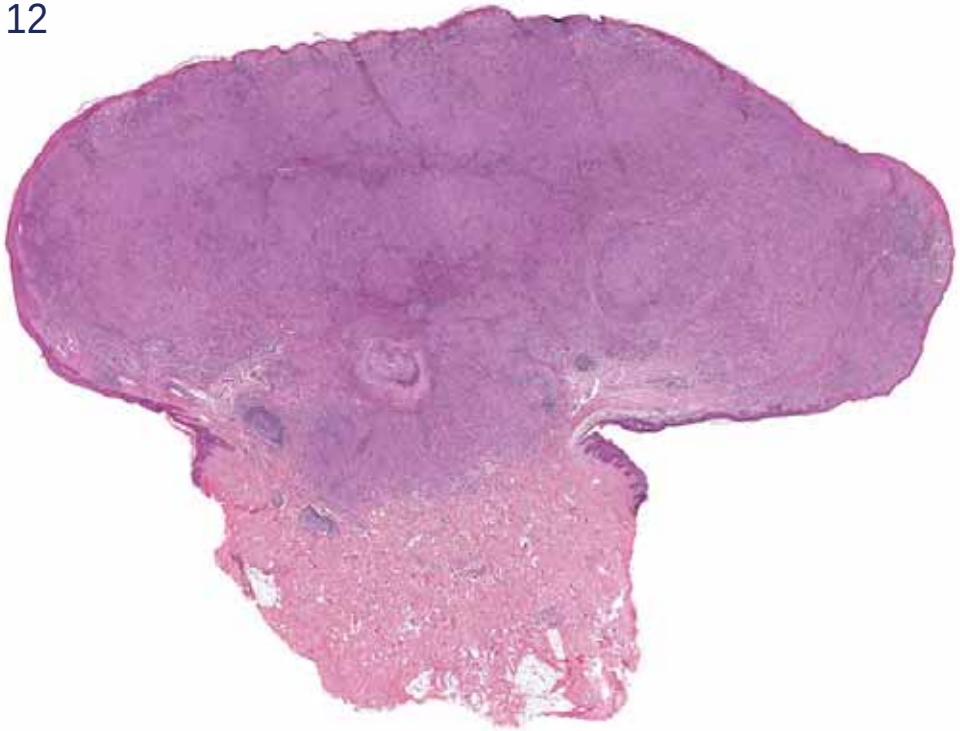

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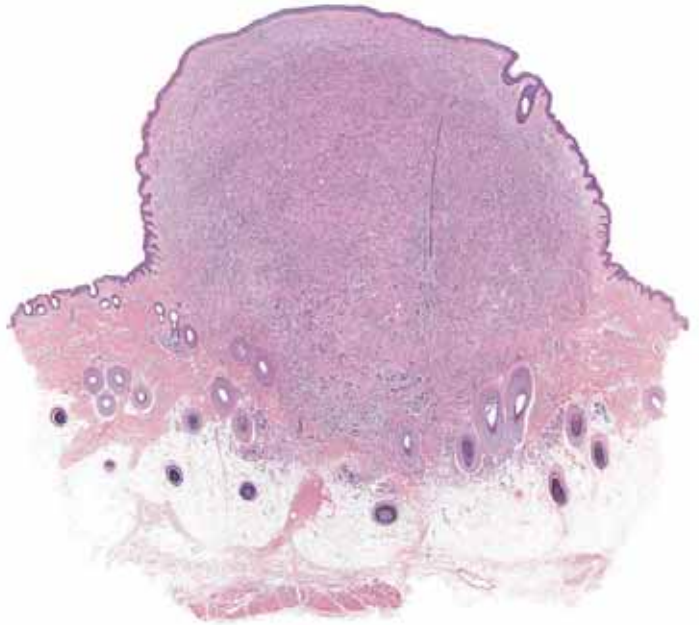

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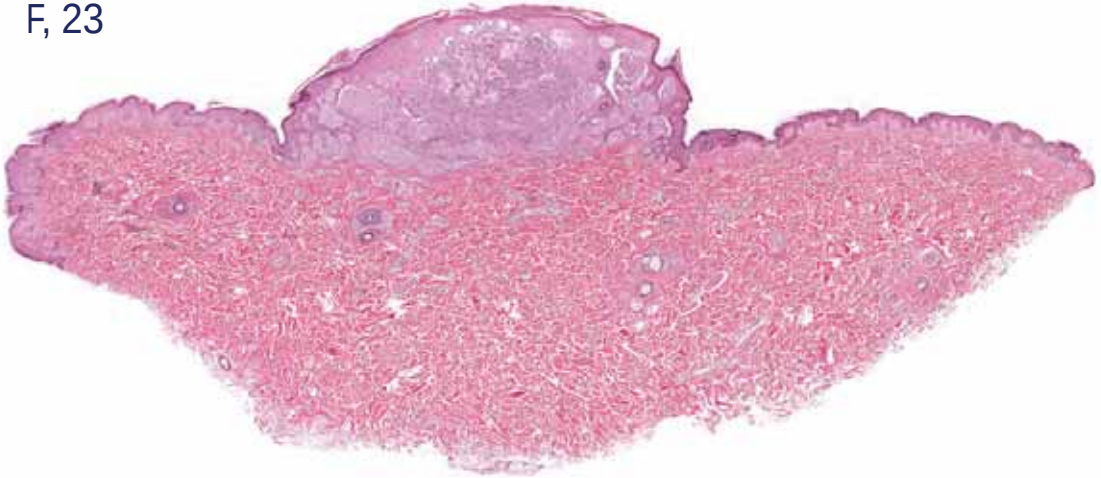

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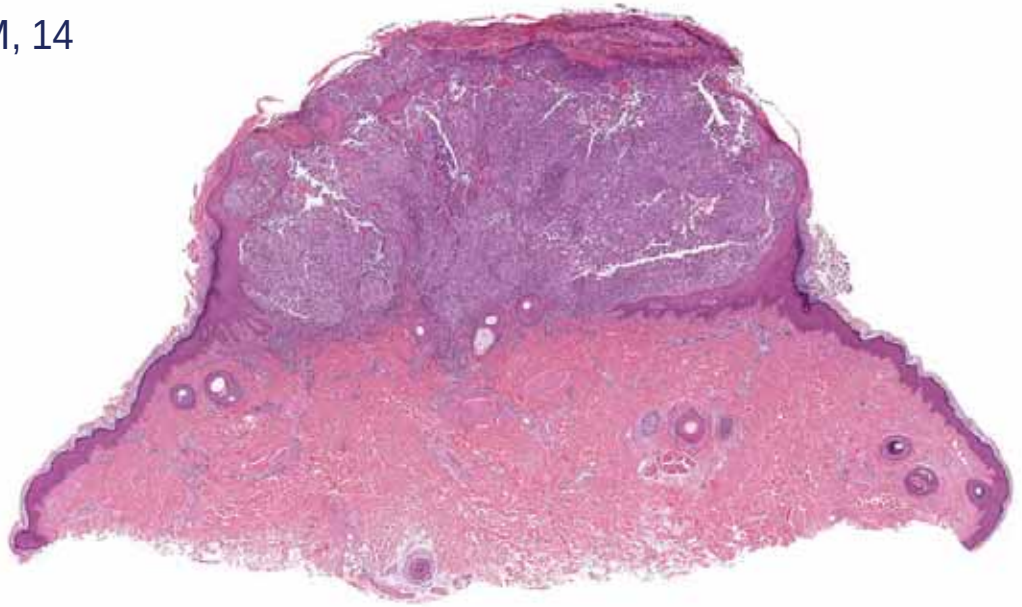
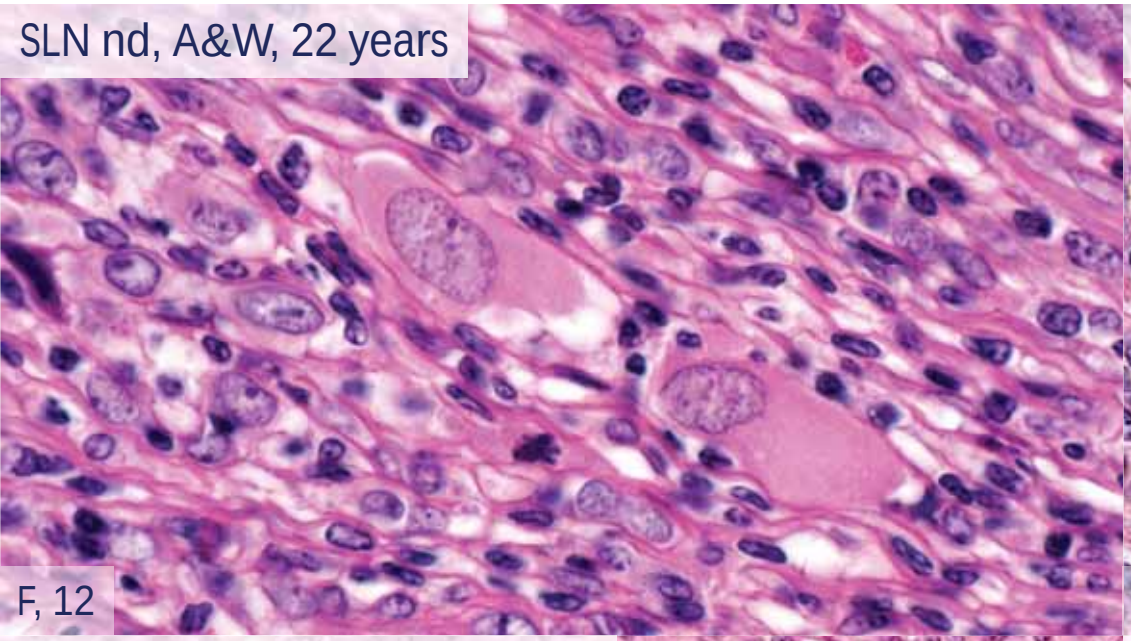
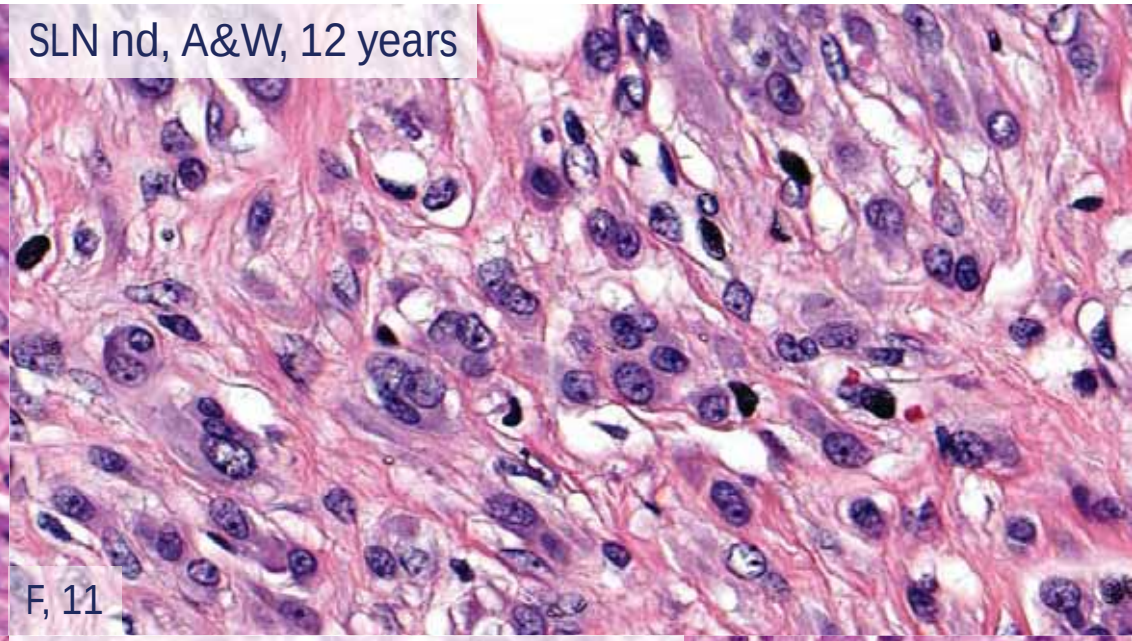
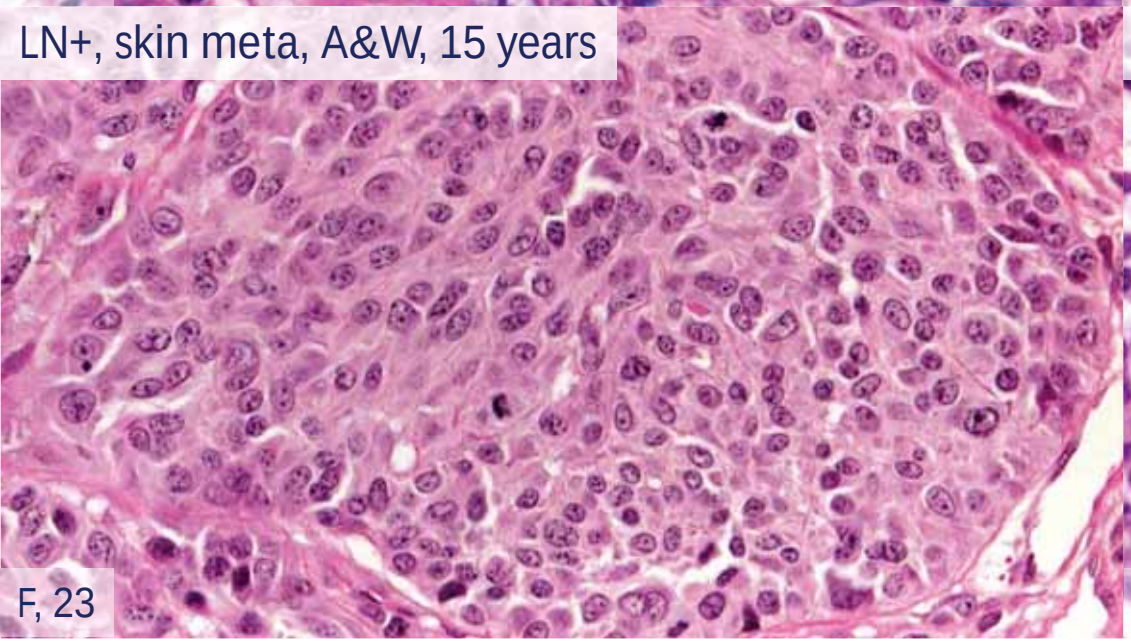
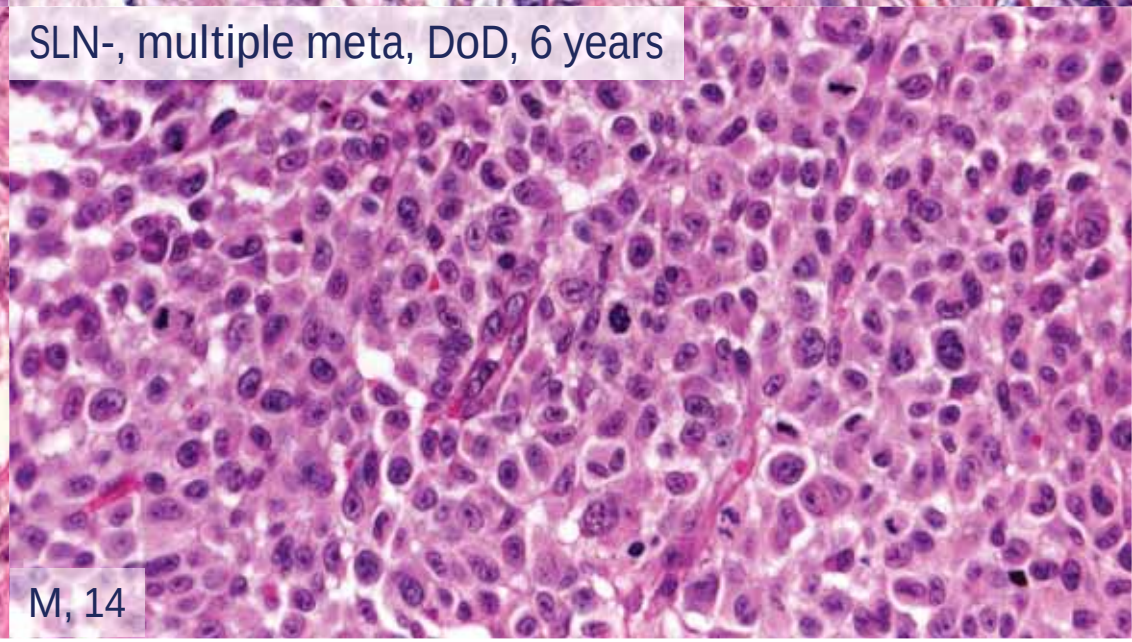



SLN nd, A&W, 22 years
F, 12


SLN nd, A&W, 12 years
F, 11


LN+, skin meta, A&W, 15 years
F, 23


SLN-, multiple meta, DoD, 6 years
M, 14

ORIGINAL ARTICLE

Melanocytic Tumors of Uncertain Malignant Potential

Results of a Tutorial Held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008

Lorenzo Cerroni, MD, Raymond Barnhill, MD,† David Elder, MD,‡ Geoffrey Gottlieb, MD,§ Peter Heenan, MD,‖ Heinz Kutzner, MD,¶ Philip E. LeBoit, MD,# Martin Mihm, Jr. MD,** Juan Rosai, MD,†† and Helmut Kerl, MD**

Abstract: Several reports demonstrated the difficulties and lack of agreement in the histopathologic diagnosis of particular melanocytic tumors (atypical Spitz tumors, atypical blue nevi, deep penetrating nevi). These lesions are often referred to as "melanocytic tumors of uncertain malignant potential" (MELTUMP). We studied a large number of such tumors to find out whether repeatable histopathologic criteria for distinction of benign from malignant cases exist. Fifty-seven cases of MELTUMP were classified within 3 groups according to behavior as follows: (a) favorable (no evidence of metastatic disease after a follow-up of ≥5 y), (b) unfavorable (tumor-related death and/or large metastatic deposits in the lymph nodes and/or visceral metastases), (c) borderline (small nodal deposits of tumor cells ≤0.2 mm). There were no significant differences in tumor thickness and presence or absence of ulceration between the different groups. The only 3 histopathologic criteria that were statistically different between the groups of favorable and unfavorable cases were presence of mitoses, mitoses near the base, and an inflammatory reaction, all of them found more frequently in cases with unfavorable behavior. The major outcome of this study of a series of "MELTUMPs" suggests as a preliminary observation that these lesions as a group exist and that they may be biologically different from conventional melanoma and benign melanocytic nevi. The terminology remains highly controversial, reflecting the uncertainty in classification and interpretation of these atypical melanocytic tumors.

Key Words: atypical Spitz tumor, malignant melanoma, melanocytic tumor of uncertain malignant potential, atypical blue nevus, deep penetrating nevus

(*Am J Surg Pathol* 2010;34:314–326)

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Melanocytic lesions continue to pose significant interpretative problems to histopathologists. Cases that were difficult to distinguish from benign melanocytic nevi have been designated by some authors as "minimal deviation melanoma" or "nevoid melanoma."[23,25–27,28] Among the most challenging problems encountered are a spectrum of relatively thick, mainly dermal tumors that are often quite difficult or impossible to distinguish from melanoma, including particularly neoplasms with spindle and/or epithelioid cells suggesting Spitz tumors, cellular and/or epithelioid blue nevi, and so-called "deep penetrating nevi."[6,13] In the last years, several reports clearly demonstrated the difficulties and lack of agreement in the histopathologic diagnosis and differential diagnosis of these particular lesions.[3–5,9,16,31,32] Two of us have previously proposed the terms "melanocytic tumor of uncertain malignant potential (MELTUMP)" or "melanocytic proliferation with indeterminate biologic potential," respectively, to reflect the uncertainty of the precise classification of such tumors.[7,14] The malignant behavior of some melanocytic tumors that had been previously classified as Spitz nevus has been described,[10] and one of us suggested that these neoplasms may represent a distinct subtype of malignant melanocytic tumors with low-grade behavior.[10,11] Finally, at several dermatopathologic meetings many anecdota cases of otherwise typical "spitzoid tumors" or "deep penetrating nevi" with lymph node and/or visceral metastases have been presented.

In October 2008 we organized a Tutorial on melanocytic tumors in the course of the XXIX Symposium of the International Society of Dermatopathology

Cases with favourable behaviour (n=17)

(no metastases, follow-up of 5 years or longer; median FU: 10y)

Unanimously diagnosed as benign:	0	
Majority favoured benign:	8	*(cum. benign dg.: 47,1%)*
Majority favoured malignant:	6	
Unanimously classified as malignant:	1	
No clear-cut majority:	2	

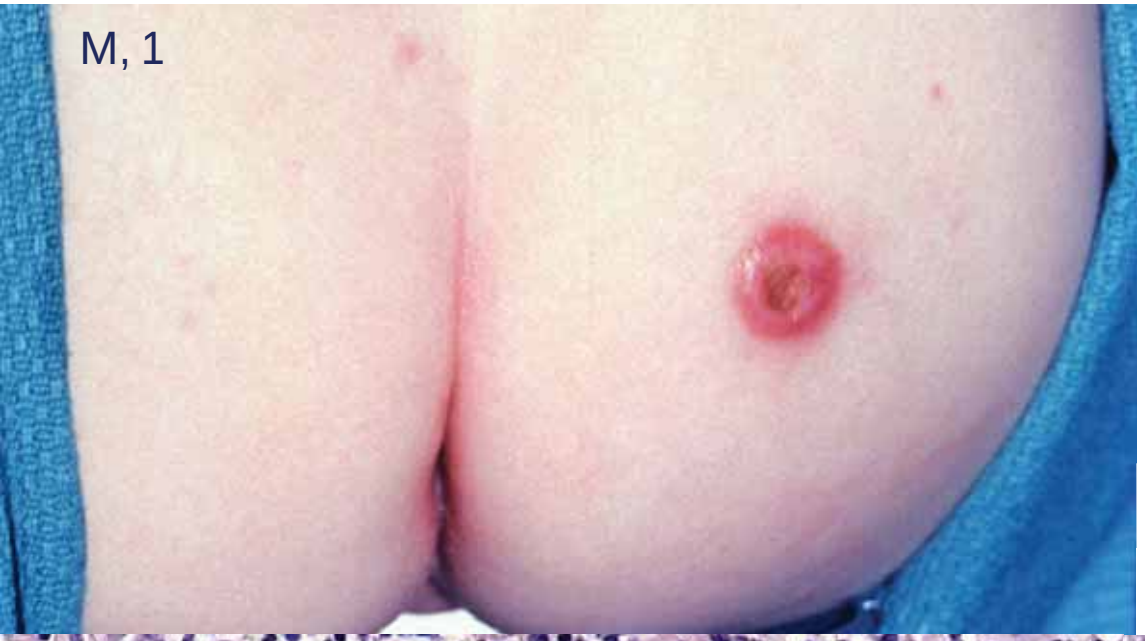
Cases with unfavourable behaviour (n=26)

(large LN metastases, or visceral metastases, or DoD)

Unanimously diagnosed as malignant:	4	*(15,4%)*
Majority favoured malignant:	15	*(cum. malignant dg.: 73,1%)*
Majority favoured benign:	6	
No clear-cut majority:	1	

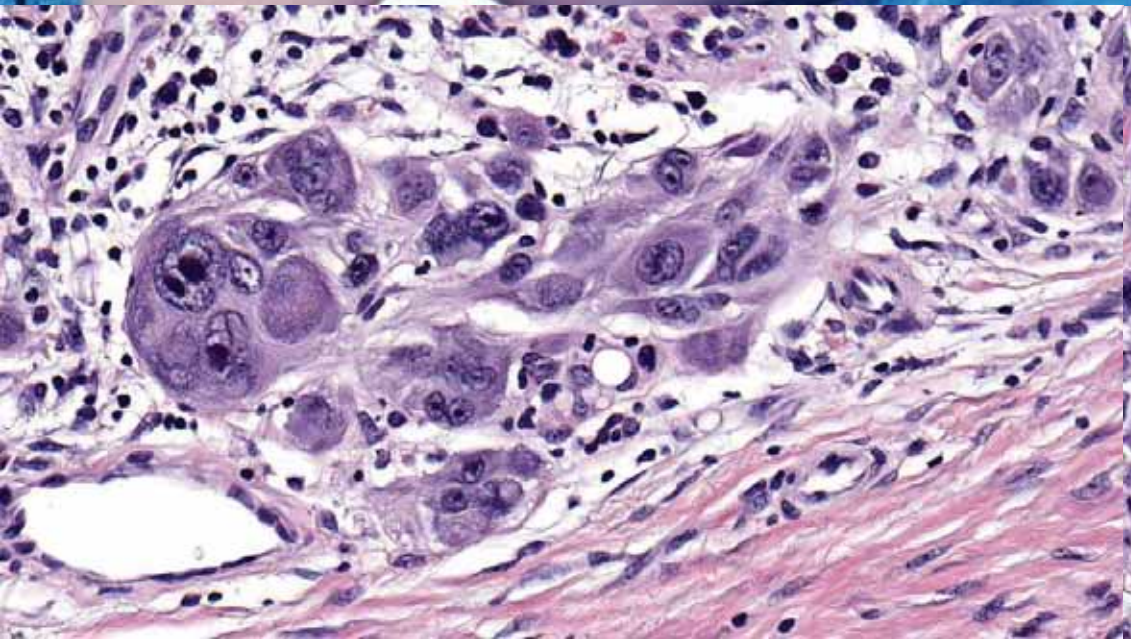
14 cases were considered biologically "borderline" (lymph nodes involved by small parenchymal clusters of melanocytes, no other evidence of disease progression)

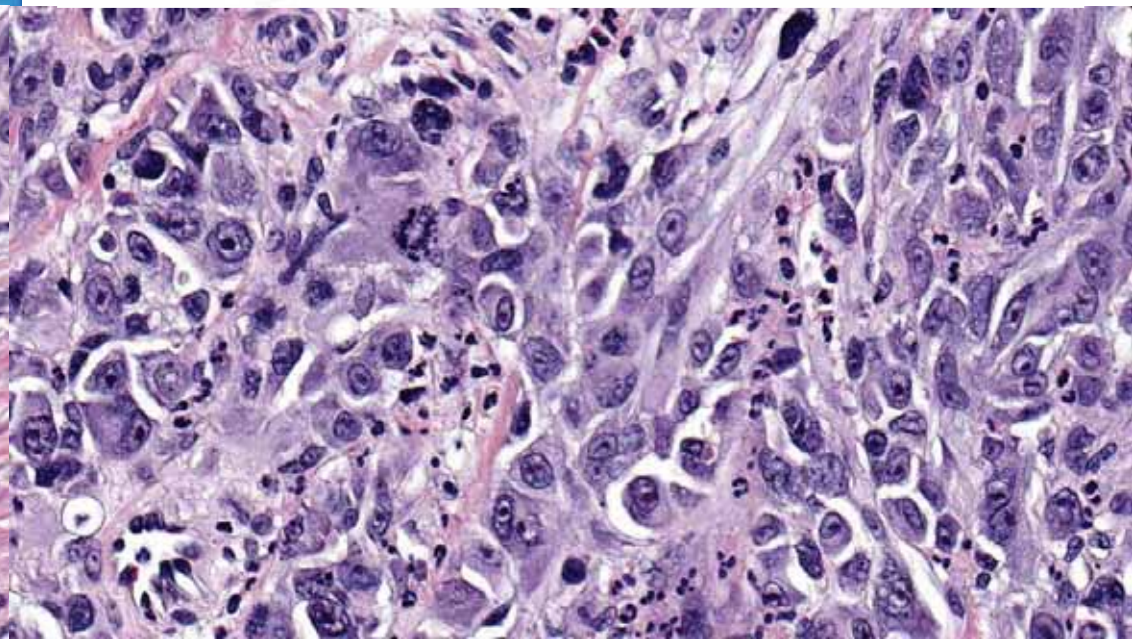
Panelists: R. Barnhill, D. Elder, G. Gottlieb, P. Heenan, H. Kutzner, P.E. LeBoit, M. Mihm, Jr., J. Rosai *(digital slides)*



Panel: 4 benign, 4 malignant

Follow-up: A&W, 22 years





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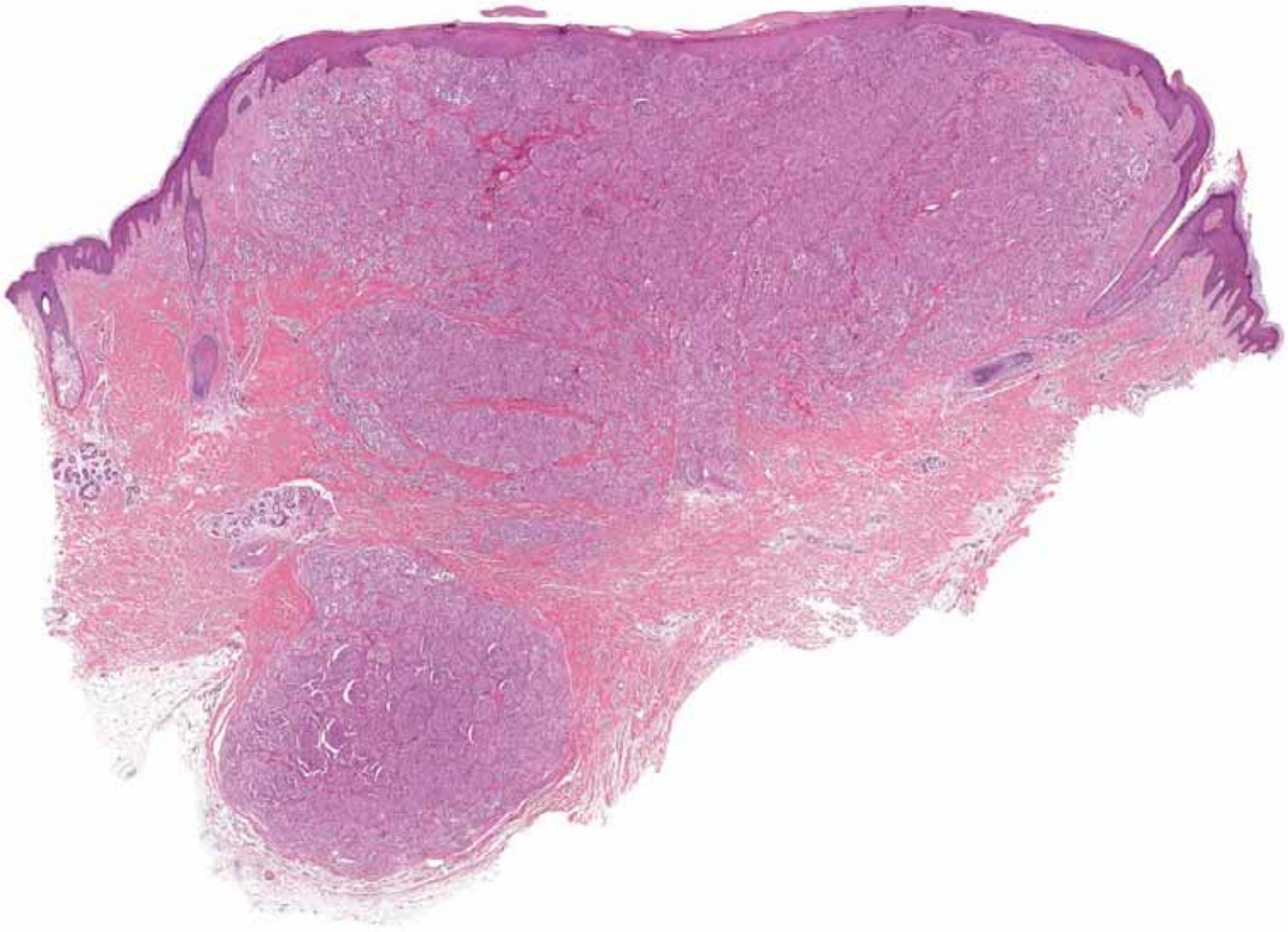
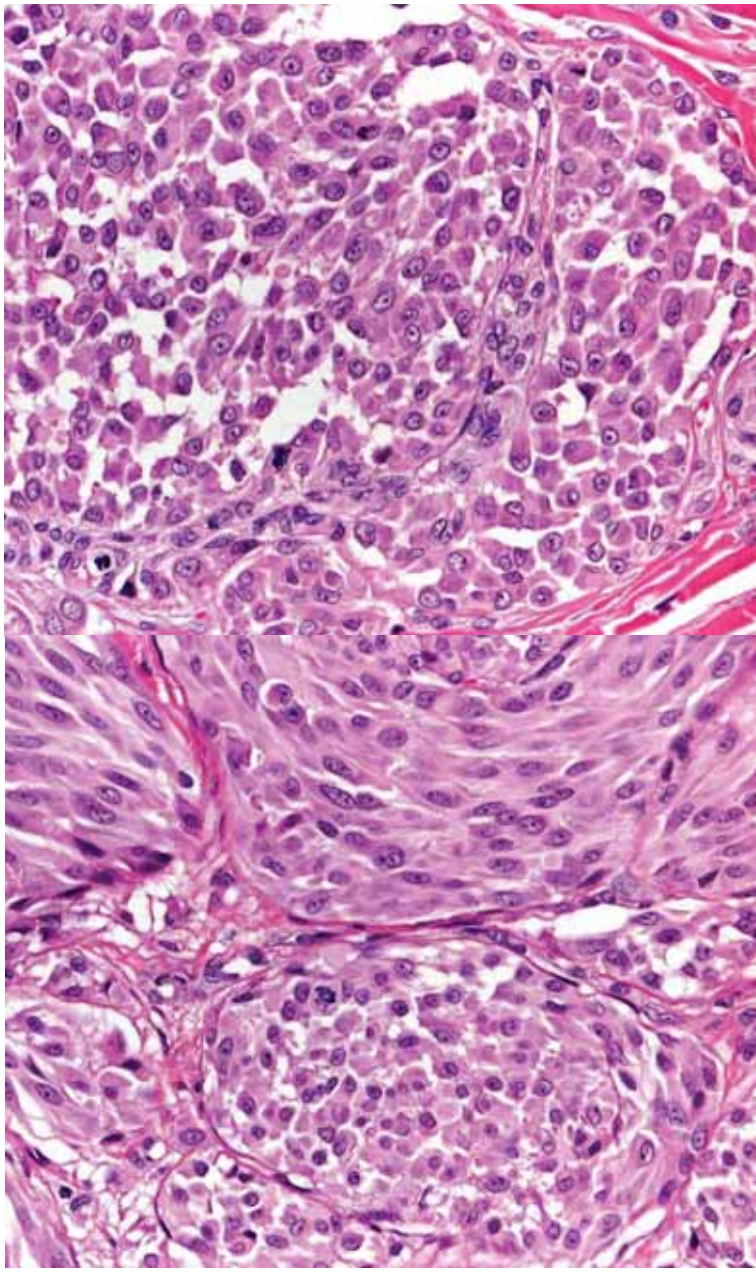
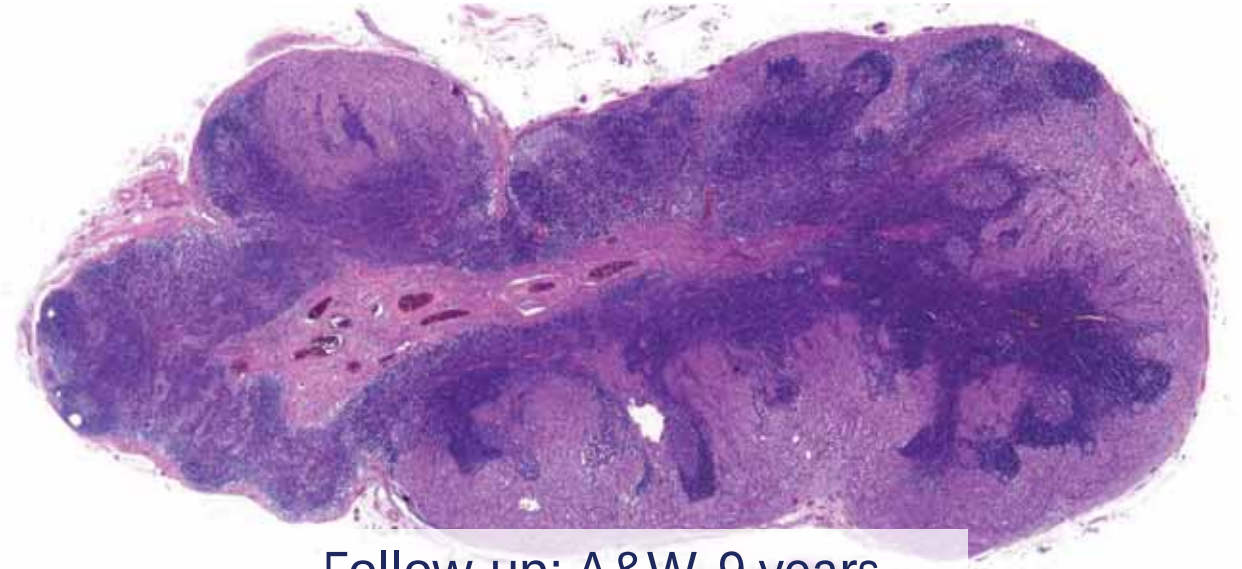
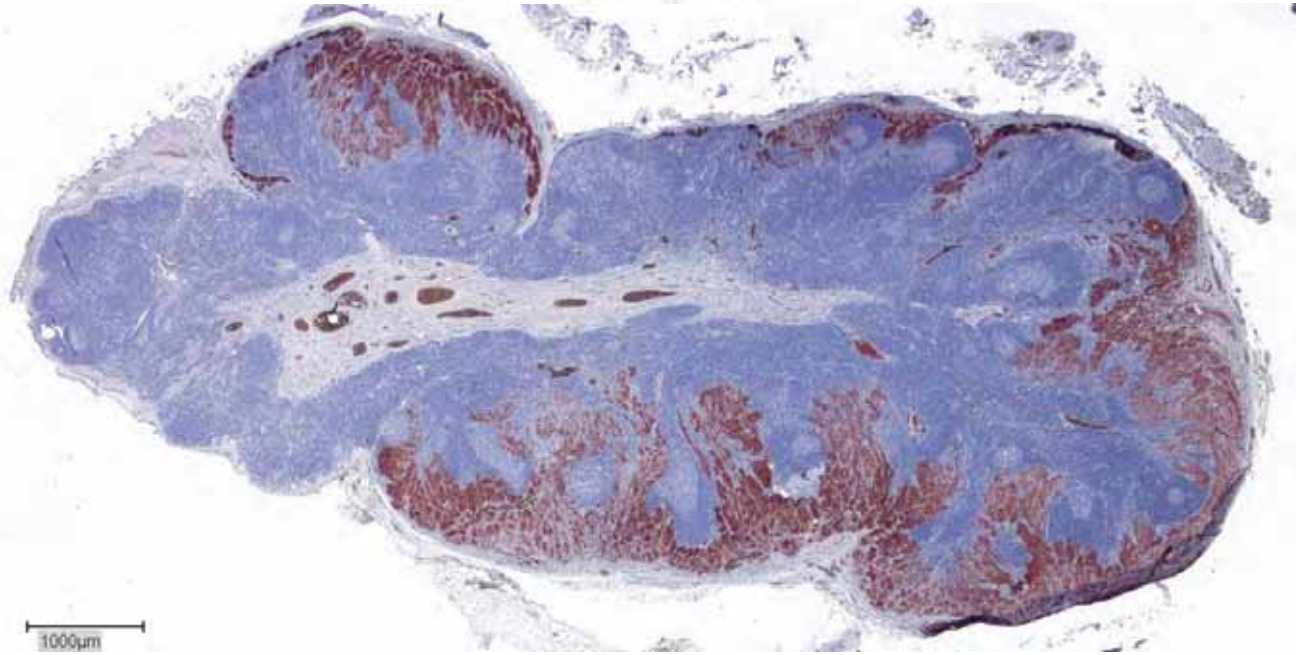


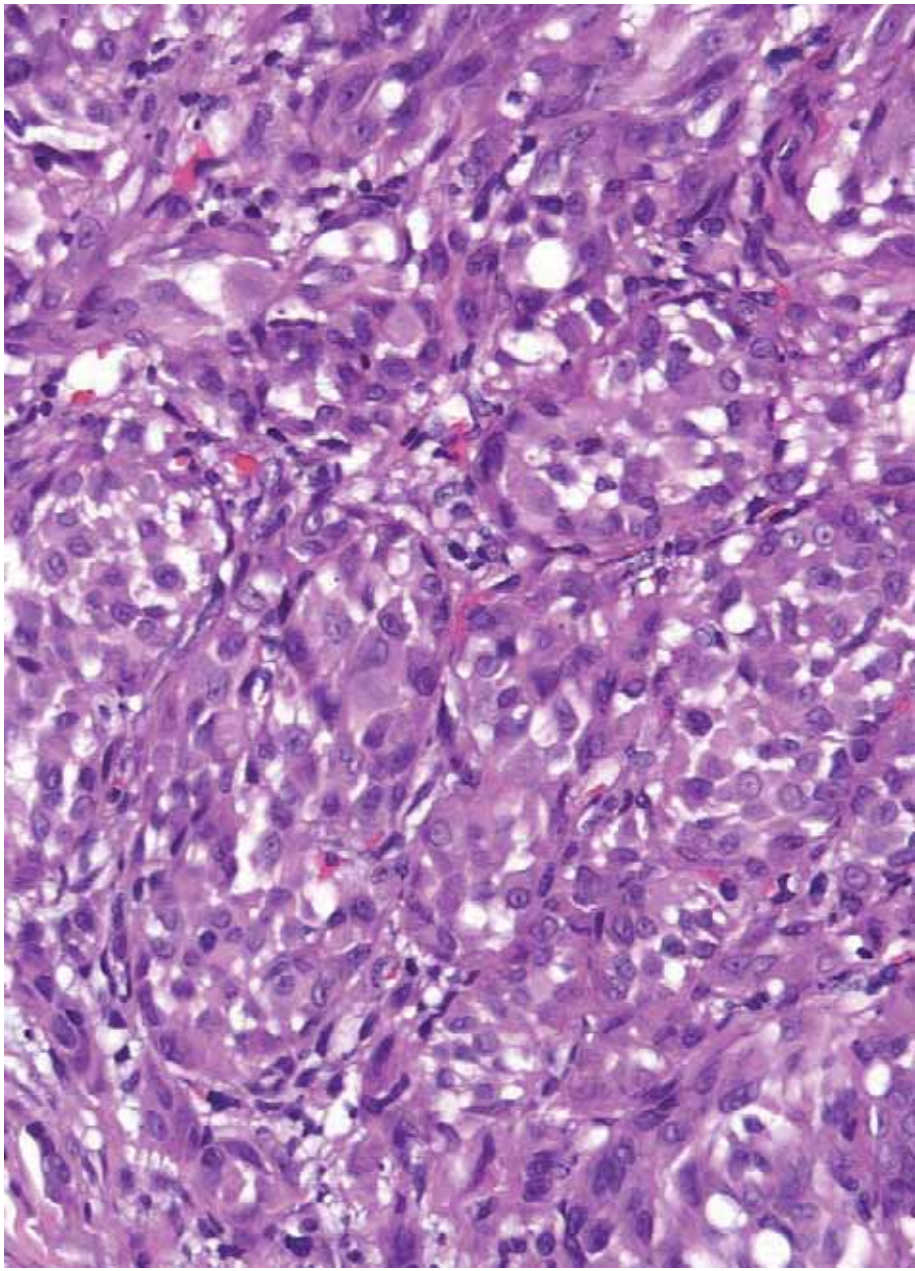


Panel: 4 benign, 3 malignant, 1 uncertain



Follow-up: A&W, 9 years





Atypical Spitz Nevi/Tumors: Lack of Consensus for Diagnosis, Discrimination From Melanoma, and Prediction of Outcome

RAYMOND L. BARNHILL, MD, ZSOLT B. ARGENYI, MD, LYNN FROM, MD, L. FRANK GLASS, MD, JOHN C. MAIZE, MD, MARTIN C. MIHM, Jr., MD, MICHAEL S. RABKIN, MD, PhD, SALVE G. RONAN, MD, WAIN L. WHITE, MD, AND MICHAEL PIEPKORN, MD, PhD

The biological nature of Spitz nevi/tumors and their diagnostic distinction from, or relationship to, melanoma remain unresolved issues. In this report, a series of 30 melanocytic lesions removed from 28 patients, including atypical Spitz nevi/tumors and metastasizing Spitzoid tumors/melanomas, were evaluated by a panel of dermatopathologists to evaluate interobserver diagnostic concordance and to assess the prognostic power of histological criteria. For inclusion in the study, each lesion had to display some criteria for the Spitz nevus, and in addition one of the following was required: (1) definitive clinical outcome such as metastasis or death of disease, or (2) long-term follow-up if the patient remained disease free. Each lesion was reviewed independently and blinded as to the clinical data by 10 pathologists, who categorized them as (1) typical Spitz nevus/tumor, (2) atypical Spitz nevus/tumor, (3) melanoma, (4) tumor with unknown biological potential, or (5) other melanocytic lesion. There was limited discussion of criteria before the review. Evaluation of 17 Spitzoid lesions yielded no clear consensus as to diagnosis; in only one case did six or more pathologists agree on a single category, regardless of clinical outcome. Notably, however, some lesions that proved fatal were categorized by most observers as either Spitz nevi or atypical Spitz tumors. Conversely, seven or more pathologists scored 13 lesions as melanoma. These results illustrate (1) substantial diagnostic difficulties posed by many Spitz tumors, especially those with atypical features, even among experts, and (2) the lack of objective criteria for their distinction from melanoma and for gauging their malignant potential. Nevertheless, our observations do suggest that a biological relationship exists between the Spitz nevus/tumor and melanoma. Hum Pathol 30:513-520. Copyright © 1999 by W.B. Saunders Company

Key words: Spitz nevus, Spitz tumors, melanoma, interobserver concordance, prognosis.

One of the more contentious issues in dermatopathology concerns the biological relationship, if any, between melanoma and the Spitz nevus/tumor. (*Melanoma* and *malignant melanoma* are used synonymously in this report; *Spitz nevus*, *Spitz's nevus*, and *Spitz tumor* are used interchangeably herein.) Although there were antecedent accounts in the literature[1] of what have come to be called Spitz nevi,[2,3] Sophie Spitz is credited with their recognition in children and with the difficulty of their histological distinction from melanoma.[4] This difficulty led to the appellation *benign juvenile melanoma*.[5] Spitz maintained that juvenile and conventional melanomas have more features in common than differences, an observation shared by many later observers.[6-10] In view of the diagnostic difficulties presented by Spitz nevi, numerous histological criteria have been proposed for their discrimination from melanoma.[3,7,8,11-18] A perusal of the literature, however, suggests that many Spitz nevi deviate from an idealized or stereotypical depiction that has been promulgated, presenting in many instances considerable difficulties with the differential diagnosis of melanoma. Complicating matters is the unsettling situation that there is no uniformity of opinion in the authoritative, classical articles with regard to the salient features that enable the reliable discrimination of the Spitz nevus from melanoma (eg, compare diagnostic criteria in Weedon and Little,[8] McWhorter and Wollner,[11] Paniago-Pereira et al,[18] and Kernen and Ackerman[18]; Table 1). Similarly, any given set of published guidelines for separating Spitz nevi from melanomas can only be presumptive, because rigorous studies with sufficient numbers of cases with long-term follow-up are not available (eg, Paniago-Pereira et al[18]) for validation of the discriminative criteria by the natural history of the disease. Moreover, practical experience suggests that these lesions clinically as well as histologically may form a continuous phenotypic spectrum overlapping that of melanoma, and it is possible and even perhaps likely that the biological potential of some Spitz nevi may defy the application of prognostic histological criteria.[6,9,10]

Most published case series of Spitz nevi are virtual tautologies, in that the investigators have collected cases retrospectively from their files, then reviewed the histological findings for the purposes of publication. In doing so, the resulting descriptions are not necessarily those of Spitz nevi per se but rather represent that unique set of criteria the authors had originally used for

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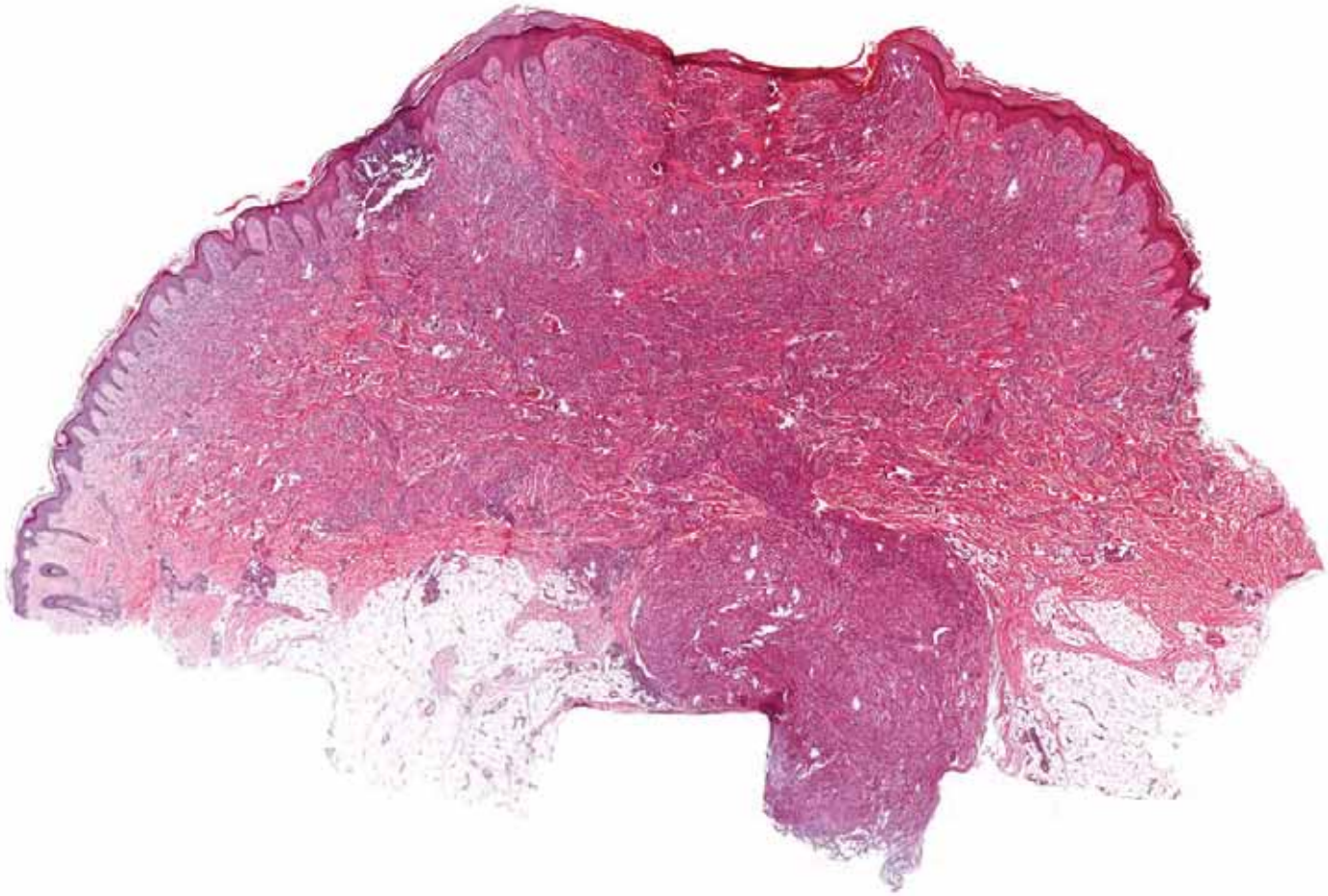
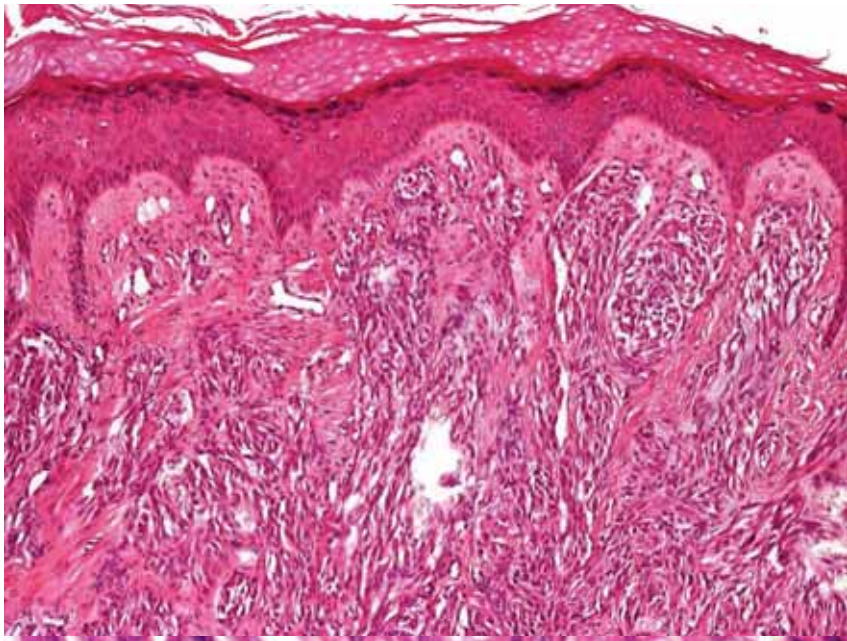
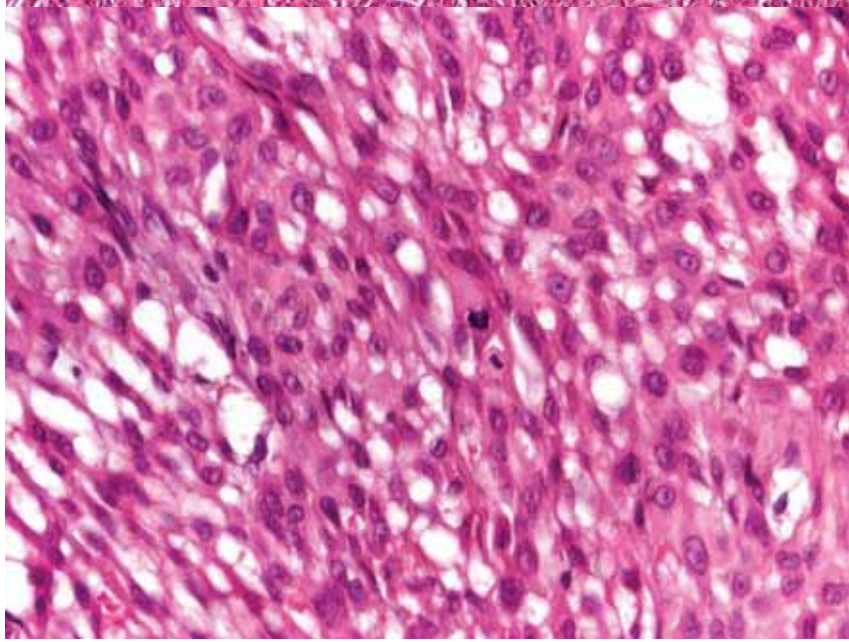
"For example, the technique of sentinel lymphadenectomy may be applied in patients with difficult to classify lesions. Although a negative sentinel node does not predict the biological behavior of the tumor, if the sentinel node contains metastatic tumor, the behavior of the tumor can be assumed to be biologically malignant until proved otherwise."

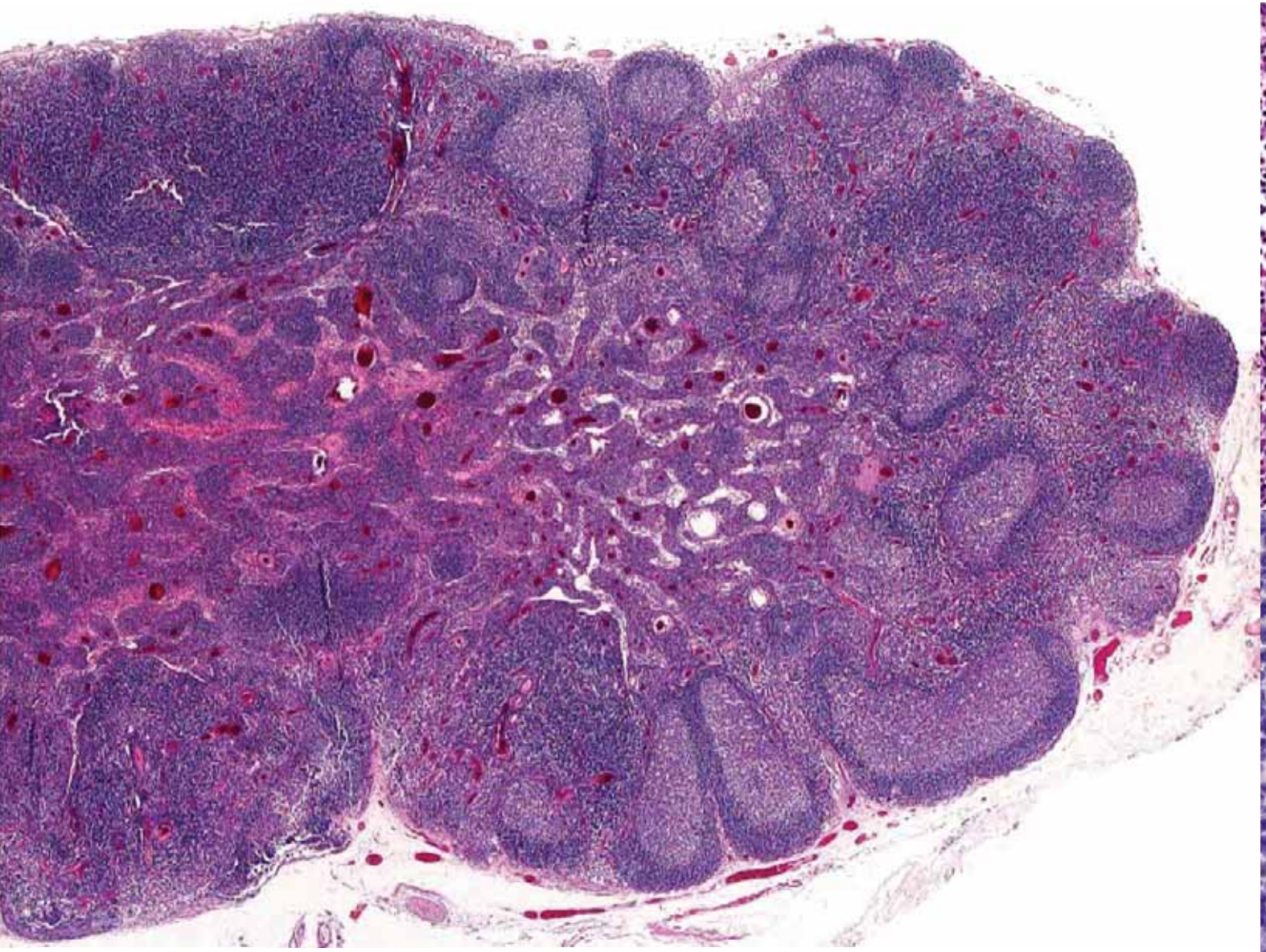
F, 4

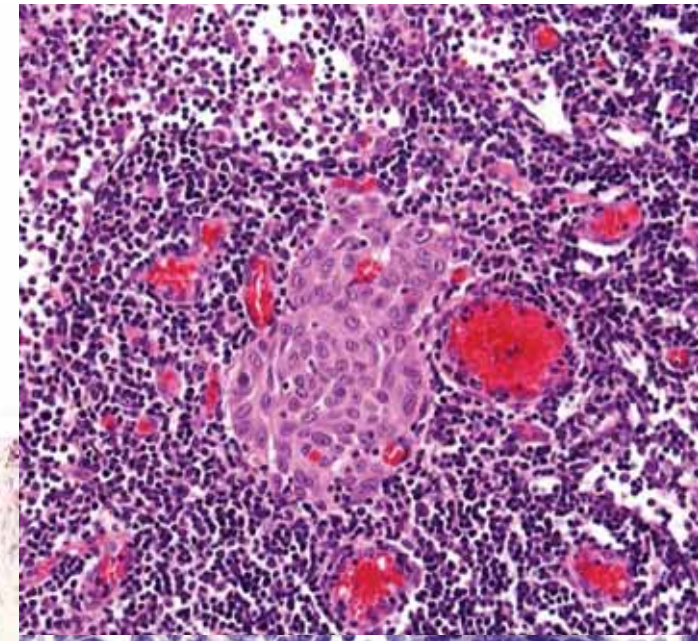


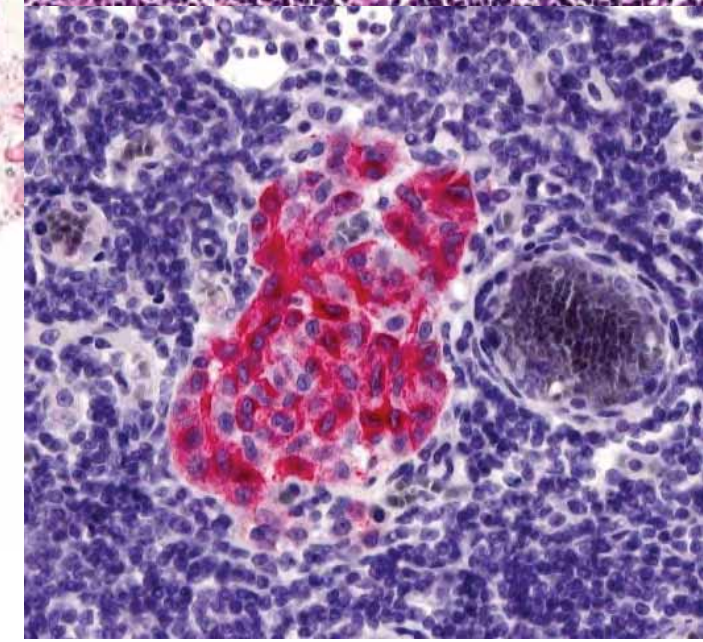




Panel: 5 benign, 1 malignant, 2 uncertain







Sentinel LN

Follow-up: A&W, 5.5 years

The American Journal of Dermatopathology 25(4): 355–356, 2003

On the Cover

What Do These Cells Prove?

Philip E. LeBoit, MD

Key Words: melanoma, metastasis, sentinel node biopsy, Spitz nevus

From the Departments of Pathology and Dermatology, University of California, San Francisco, California.

A patient has an unusual melanocytic proliferation. Skilled observers are puzzled—is it a Spitz's nevus or a melanoma? The patient and the dermatologist want to know, and with certainty. Why not do a sentinel node biopsy to find out?

Certainly, this question has been asked and answered before. Several reports now tell of cases in which diagnostic uncertainty was settled by means of a sentinel node biopsy.[1–3] But is this an accurate approach?

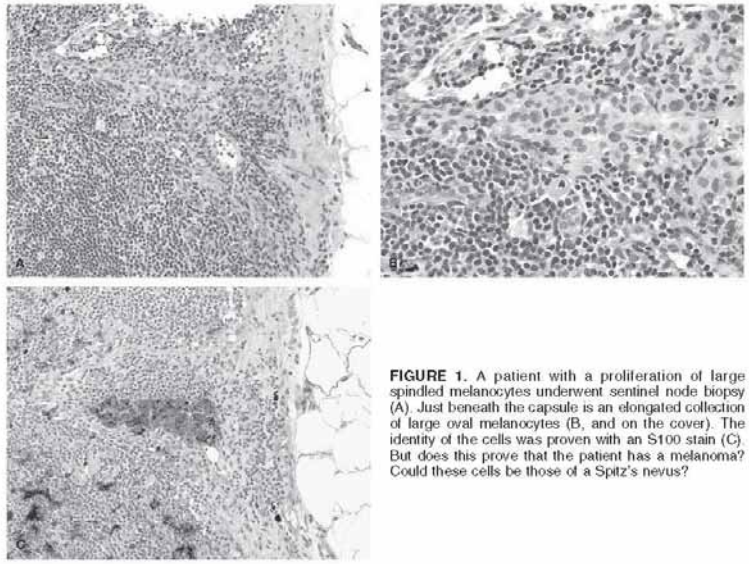


FIGURE 1. A patient with a proliferation of large spindled melanocytes underwent sentinel node biopsy (A). Just beneath the capsule is an elongated collection of large oval melanocytes (B, and on the cover). The identity of the cells was proven with an S100 stain (C). But does this prove that the patient has a melanoma? Could these cells be those of a Spitz's nevus?

Certainly, if a patient with an ambiguous neoplasm has a sentinel lymph node packed with anaplastic-appearing melanocytes, with many mitotic figures and zones of necrosis, you will get no argument from me (although such a node is usually palpable). On the other hand, what if the node shows only a small cluster of large melanocytes (on the cover, and Fig. 1)? What then?

So what do the melanocytes in the lymph node on the cover prove? To some, everything—a sure diagnosis of melanoma. To me, nothing.

Molecular Cytogenetic Analysis of Spitz Nevi Shows Clear Differences to Melanoma

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Spitz nevus is a benign neoplasm of melanocytes that can be difficult or impossible to distinguish from melanoma by clinical and histopathologic examination. We studied genomic DNA from 17 Spitz nevi by comparative genomic hybridization (CGH). Thirteen lesions showed no chromosomal aberrations, three cases had a gain involving the entire p-arm of chromosome 11, and one case showed a gain of chromosome 7q21-qter. Fluorescence *in situ* hybridization (FISH) on lesional tissue with a probe for the p-arm of chromosome 11 showed 6–10 p-arm signals per nucleus in those cases with a CGH-detected gain of chromosome 11p. One case with a normal CGH profile also showed increased copy number of 11p by FISH. Thus, the majority of Spitz nevi have a normal chromosomal complement at the level of CGH resolution; however some may contain gains, with 11p apparently being the most frequently involved location. These findings differ significantly from the previously reported changes in primary cutaneous melanoma, which show frequent deletions of chromosomes 9p (82%), 10q (63%), 6q (28%), and 8p (22%), as well as gains of chromosomes 7 (50%), 8 (34%), 6p (28%), 1q (25%) by CGH analysis. These clear differences in the location and frequencies of chromosomal aberrations in Spitz nevi and primary cutaneous melanomas could represent a basis for developing adjunctive techniques for refining accuracy in the difficult differential diagnosis of spitzoid melanocytic neoplasms. *Key words: comparative genomic hybridization/epitheloid and spindle cell pathology/genetics/skin neoplasms. J Invest Dermatol 113:1065–1069, 1999*

Spitz nevi are benign melanocytic neoplasms that can resemble melanoma on histopathologic examination. They were first described as "juvenile melanoma" by Sophie Spitz in 1948 and were initially regarded as a subset of childhood melanoma that follows a benign course (Spitz, 1948). Spitz nevi account for about 1% of surgically removed melanocytic nevi (Casso *et al*, 1992).

Although in general the pathologic diagnosis of Spitz nevus can be reliably achieved by conventional histopathologic criteria, there is a subset of cases in which it is difficult or impossible to differentiate Spitz nevi from melanoma. Both Spitz nevi and melanoma can be composed of melanocytes with abundant cytoplasm and large nuclei. These nuclei can be pleomorphic and contain macronucleoli. Mitotic figures, sometimes numerous, occur in both neoplasms.

Misdiagnosis of Spitz nevus as melanoma and vice versa has been repeatedly reported (Okun, 1979; Goldes *et al*, 1984; Peters and Goellner, 1986). A retrospective study of 102 melanocytic tumors occurring in patients under age 17, which were originally diagnosed as melanoma, found that only 60 cases were classified as melanoma after re-examination by a panel of experts (Spitz *et al*, 1996). Forty-two lesions were reclassified as nevi, 22 of those as Spitz nevi. The hazard of mistaking a Spitz nevus for melanoma is that the patient may be subjected to needless surgery and adjunctive therapy, become unable to plan for the future, be psychologically traumatized, and have difficulties in obtaining health insurance. For obvious reasons the misdiagnosis of a melanoma as nevus can have even more dramatic sequela. The difficulties in differentiating Spitz nevi from melanoma and the consequences of underdiagnosis lead some authors to propose that Spitz nevi and melanoma represent a continuum of disease (Casso *et al*, 1992).

We recently reported on frequent losses of chromosomes 9 and 10 as well as gains of chromosomes 7, 8q, and 6p in primary cutaneous melanoma (Bastian *et al*, 1998). The purpose of this study was the characterization of genomic aberrations in Spitz nevi using comparative genomic hybridization (CGH) (Kallioniemi *et al*, 1992) as an unbiased genome scanning approach to identify potential differences to melanoma.

MATERIALS AND METHODS

Tumor material Formalin-fixed, paraffin-embedded tissue from Spitz nevi from 17 patients were retrieved from the archives of the Department of Dermatology (University Hospital, Würzburg, Germany) and the Dermatopathology Section, Departments of Pathology and Dermatology (University of California, San Francisco). We selected lesions in which the histopathologic diagnosis was unequivocal using widely agreed upon criteria, had an extensive and densely cellular dermal component that allowed the collection of mostly melanocytes (>50%), and had at most a sparse lymphocytic infiltrate, so that lymphocyte DNA would not obscure aberrations in the neoplastic cells.

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Abbreviations: CGH, comparative genomic hybridization; FISH, fluorescence *in situ* hybridization.

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

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

Boris C. Bastian,*† Philip E. LeBoit,*† and Daniel Pinkel†

debate whether Spitz nevus and melanoma reside at the opposing ends of a biological spectrum[2] or represent two

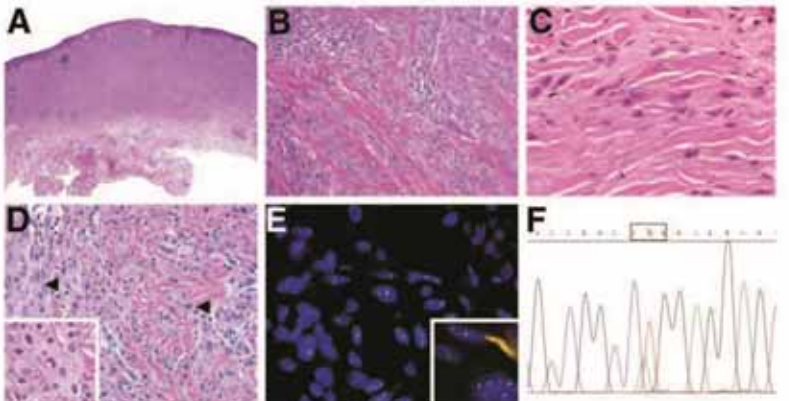
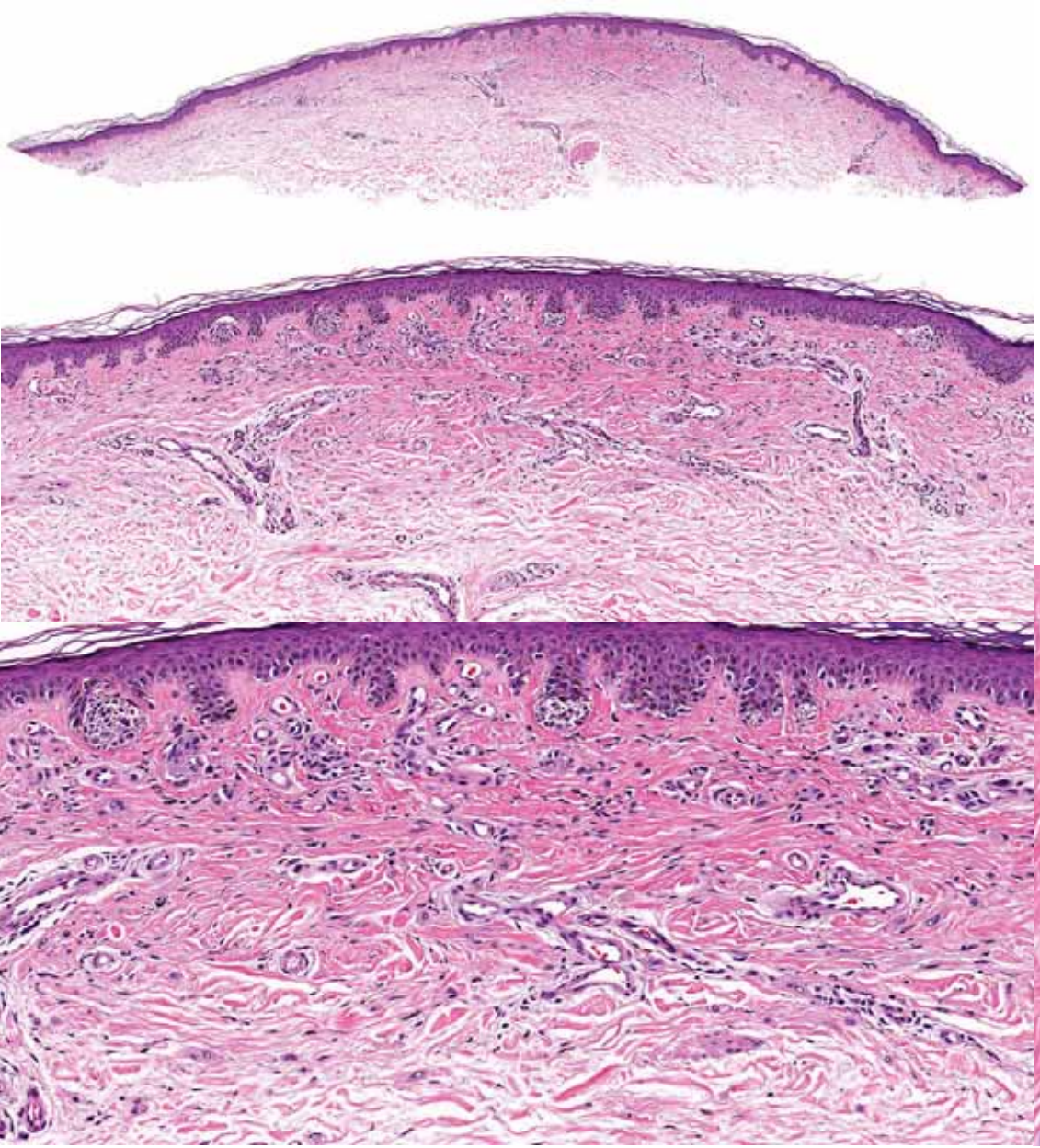


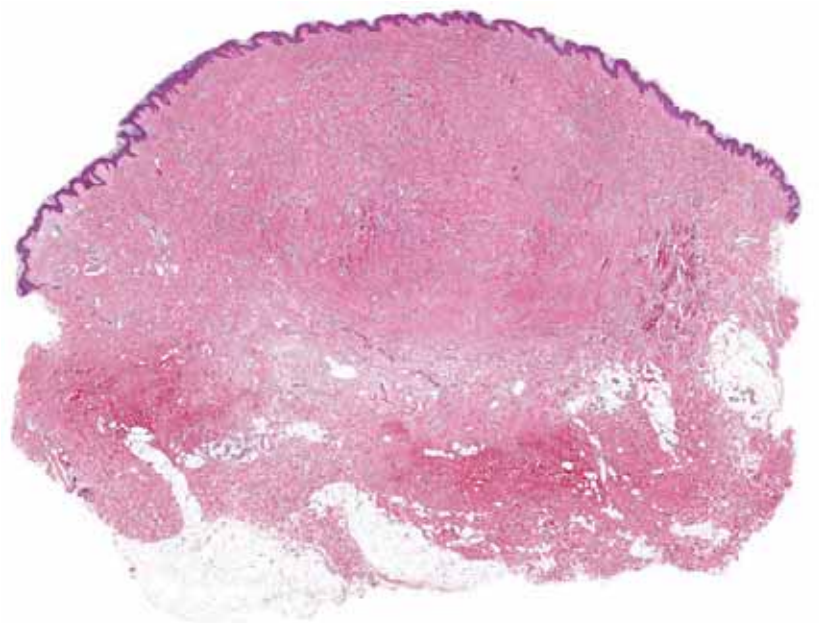
Figure 1. Histological features associated with copy number increase of 11p (A–D). A: Compound, predominantly intradermal Spitz nevus. B: Melanocytes with ample amphophilic cytoplasm and vesicular nuclei with prominent nucleoli between haphazardly arranged collagen fibers. C: Melanocytes with pleomorphic nuclei singly and in clusters between thickened collagen fibers. D: Cells are surrounded by a fine eosinophilic rim (arrowheads and inset). E: Dual-color FISH with a probe containing HRAS (green signals) and a reference probe for chromosome 11q (red signals) showing a central nest of melanocytes with multiple green signals surrounded by normal cells. F: Sequence profile of a portion of exon 2 of HRAS showing a A→T mutation of codon 61 (bound).

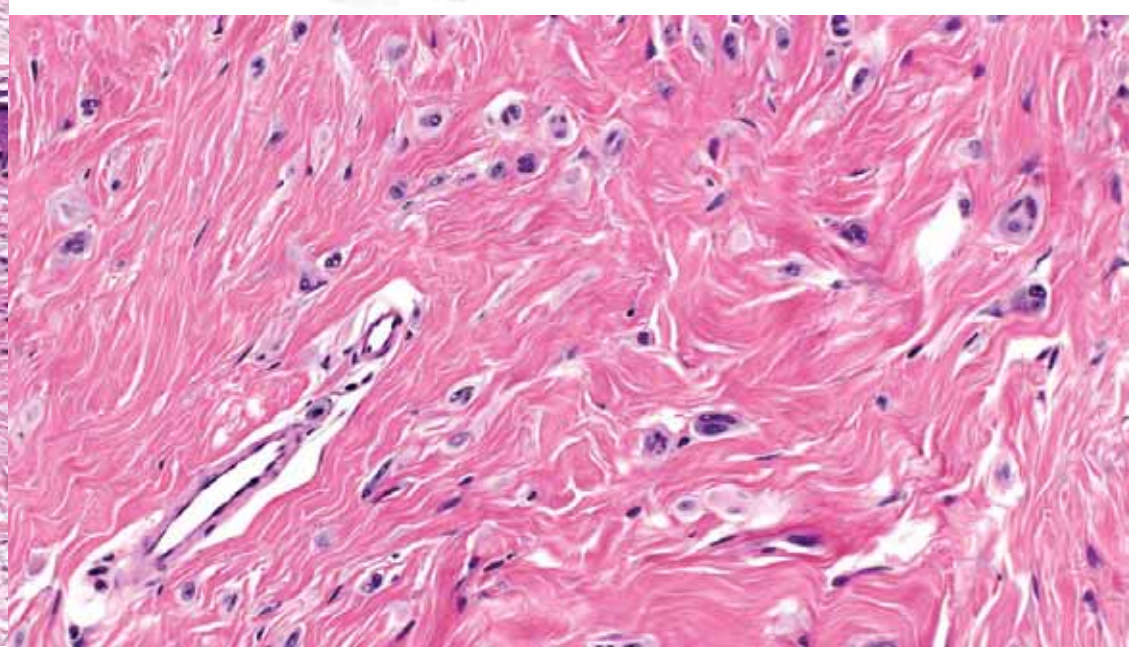
netic alterations drives the partially transformed me-

partments of Dermatology and Pathology at the Univer-

Tumors with 11p copy number increases were larger, predominantly intradermal, had marked desmoplasia, characteristic cytological features, and had an infiltrating growth pattern.







nature COMMUNICATIONS

ARTICLE

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Kinase fusions are frequent in Spitz tumours and spitzoid melanomas

Thomas Wiesner[1,2,*], Jie He[3,*], Roman Yelensky[3,*], Rosaura Esteve-Puig[4], Thomas Botton[4], Iwei Yeh[4], Doron Lipson[3], Geoff Otto[3], Kristina Brennan[3], Rajmohan Murali[5,6], Maria Garrido[4], Vincent A. Miller[3], Jeffrey S. Ross[3], Michael F. Berger[1], Alyssa Sparatta[4], Gabriele Palmedo[7], Lorenzo Cerroni[7], Klaus J. Busam[5], Heinz Kutzner[7], Maureen T. Cronin[3], Philip J. Stephens[3] & Boris C. Bastian[1,4,5]

Spitzoid neoplasms are a group of melanocytic tumours with distinctive histopathological features. They include benign tumours (Spitz naevi), malignant tumours (spitzoid melanomas) and tumours with borderline histopathological features and uncertain clinical outcome (atypical Spitz tumours). Their genetic underpinnings are poorly understood, and alterations in common melanoma-associated oncogenes are typically absent. Here we show that spitzoid neoplasms harbour kinase fusions of *ROS1* (17%), *NTRK1* (16%), *ALK* (10%), *BRAF* (5%) and *RET* (3%) in a mutually exclusive pattern. The chimeric proteins are constitutively active, stimulate oncogenic signalling pathways, are tumourigenic and are found in the entire biologic spectrum of spitzoid neoplasms, including 55% of Spitz naevi, 56% of atypical Spitz tumours and 39% of spitzoid melanomas. Kinase inhibitors suppress the oncogenic signalling of the fusion proteins in vitro. In summary, kinase fusions account for the majority of oncogenic aberrations in spitzoid neoplasms and may serve as therapeutic targets for metastatic spitzoid melanomas.

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Table 1 | Frequency of kinase fusions in spitzoid neoplasms.

Fusion	Spitz naevus ($n=75$) % (number of cases)	Atypical Spitz tumour ($n=32$) % (number of cases)	Spitzoid melanoma ($n=33$) % (number of cases)	Total ($n=140$) % (number of cases)
ROS1	25.3 (19)	6.3 (2)	9.1 (3)	17.1 (24)
ALK	10.7 (8)	15.6 (5)	3 (1)	10 (14)
NTRK1	10.7 (8)	25 (8)	21.2 (7)	16.4 (23)
BRAF	5.3 (4)	6.3 (2)	3 (1)	5 (7)
RET	2.7 (2)	3.1 (1)	3 (1)	2.9 (4)
Total	54.7 (41)	56.3 (18)	39.4 (13)	51.4 (72)

"Spitzoid neoplasms harbour kinase fusions of *ROS1* (17%), *NTRK1* (16%), *ALK* (10%), *BRAF* (5%) and *RET* (3%) in a mutually exclusive pattern. The chimeric proteins are constitutively active, stimulate oncogenic signalling pathways, are tumourigenic *and are found in the entire biologic spectrum of spitzoid neoplasms, including 55% of Spitz naevi, 56% of atypical Spitz tumours and 39% of spitzoid melanomas.*"

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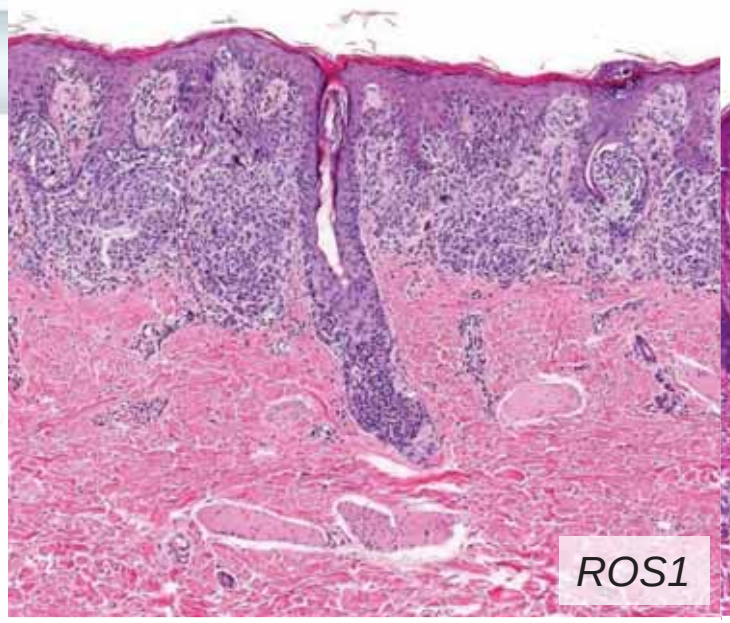

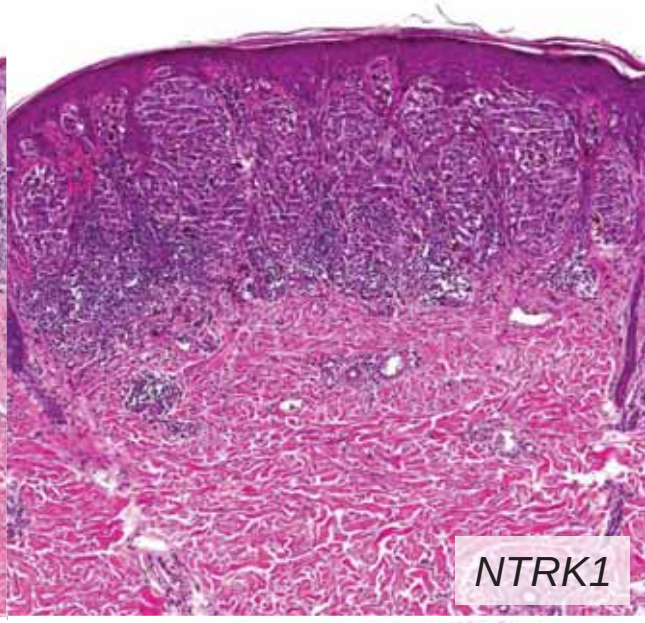

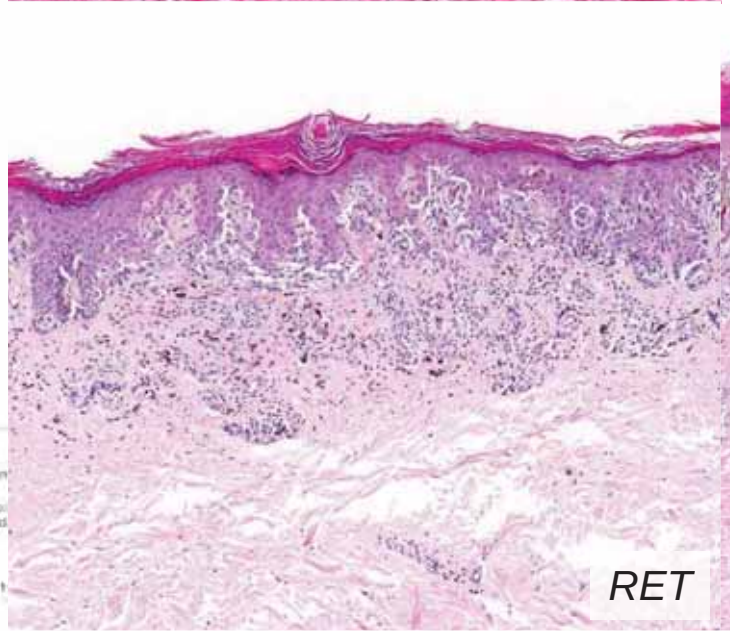

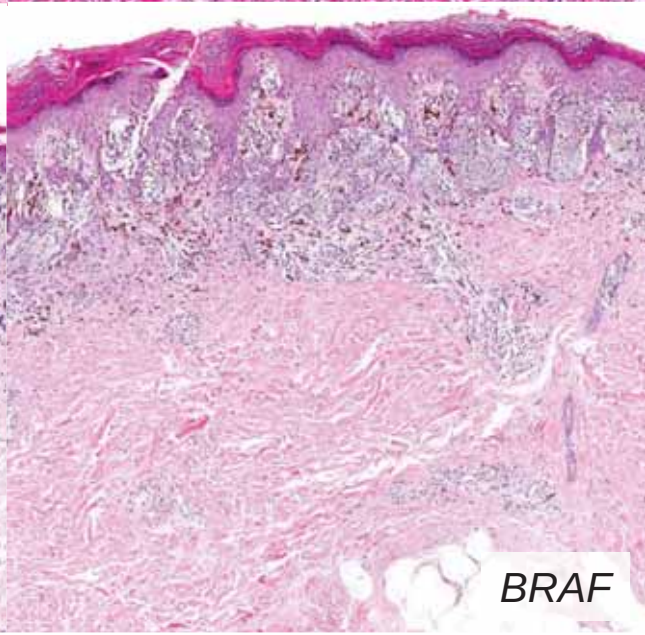

Clinical and Pathologic Findings of Spitz Nevi and Atypical Spitz Tumors With *ALK* Fusions

Klaus J. Busam, MD, Heinz Kutzner, MD,† Lorenzo Cerroni, MD,‡ and Thomas Wiesner, MD‡§*

Abstract: Spitz tumors represent a group of melanocytic neoplasms that typically affect young individuals. Microscopically, the lesions are composed of cytologically distinct spindle and epithelioid melanocytes, with a range in the architectural display or the cells, their nuclear features, and secondary epidermal or stromal changes. Recently, kinase fusions have been documented in a subset of Spitz tumors, but there is limited information on the clinical and pathologic features associated with those lesions. Here, we report a series of 17 patients (9 male, 8 female) with spitzoid neoplasms showing *ALK* fusions (5 Spitz nevi and 12 atypical Spitz tumors). The patients' ages ranged from 2 years to 35 years (mean = 17 y; median = 16 y). Most lesions were located on the lower extremities and presented clinically as polypoid nodules. All tumors were compound melanocytic proliferations with a predominant intradermal growth. Tumor thickness ranged from 1.1 to 6 mm (mean = 2.9 mm; median = 2.5 mm). The most characteristic histopathologic feature of the tumors (seen in all but 2 lesions) was a plexiform dermal growth of intersecting fascicles of fusiform melanocytes. All but 2 tumors were amelanotic. All tumors were strongly immunoreactive for ALK. The *ALK* rearrangements were confirmed in all cases by fluorescence in situ hybridization (FISH), and the fusion partner was determined by quantitative polymerase chain reaction as *TPM3* (*tropomyosin 3*) in 11 cases and *DCTN1* (*dynactin 1*) in 6 cases. None of the 8 tumors that were analyzed by FISH for copy number changes of 6p, 6q, 9p, or 11q met criteria for melanoma. Two patients underwent a sentinel lymph node biopsy, and in both cases melanocyte nests were found in the subcapsular sinus of the node. Array comparative genomic hybridization of these 2 tumors revealed no chromosomal gains or losses. In conclusion, our study revealed that Spitz nevi/tumors with *ALK* rearrangement show a characteristic plexiform morphology and that *ALK* immunohistochemistry and FISH enable the accurate identification of this morphologic and genetic distinct subset of spitzoid neoplasms.

Key Words: kinase fusion, melanocytic nevus, Spitz nevus, ALK

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Spitzoid melanocytic neoplasms include Spitz nevi (benign tumors), so-called "atypical Spitz tumors" (tumors of uncertain malignant potential), and "spitzoid" melanomas (malignant tumors, with metastasizing and lethal potential[1]). They remain a problem area in the field of dermatopathology because of the difficulty in distinguishing the relatively more common indolent lesions from the rare metastasizing and lethal spitzoid melanoma. However, significant progress has been made over the past decade regarding cytogenetic and/or molecular alterations of these tumors.[2–7] A number of subsets of Spitz tumors have been identified with distinct, clinical, pathologic, and genetic features. They include the *HRAS*-mutant sclerosing Spitz nevi,[2] the *BAP1*^{loss} Spitz tumors,[7–9] and the spitzoid melanomas with homozygous deletions of p16.[6]

An important milestone in our understanding of Spitz tumors is the recent discovery that some of them harbor gene fusions involving receptor tyrosine kinases *ALK*, *ROS1*, *NTRK1*, and *RET* or the serine-threonine kinase *BRAF*.[10] Such gene rearrangements were found in 72 of 140 (51.4%) spitzoid neoplasms. Fourteen of these 140 (10%) spitzoid neoplasms showed *ALK* fusions. All kinase fusions were mutually exclusive and occurred only in tumors without *HRAS* mutations or loss of *BAP1*. Kinase fusions were detected across the entire spectrum of Spitz lesions (benign Spitz nevi, atypical Spitz tumors, and rare spitzoid melanomas), which suggests that the fusions likely occur early in the pathogenesis of the tumors and are per se not sufficient for malignant transformation. This observation is analogous to that of mutations in oncogenes (such as *BRAF*, *NRAS*, *GNAQ*, and *GNA11*) commonly found in melanocytic neoplasms.[4,7,11,12]

Currently, it is unknown whether or not any of the translocation-associated Spitz tumors have distinct clinical and/or pathologic features. It is also unknown whether the presence or absence of a kinase fusion of a particular type is associated with a more indolent or aggressive clinical course. In this study, we document clinical findings and describe the spectrum of microscopic

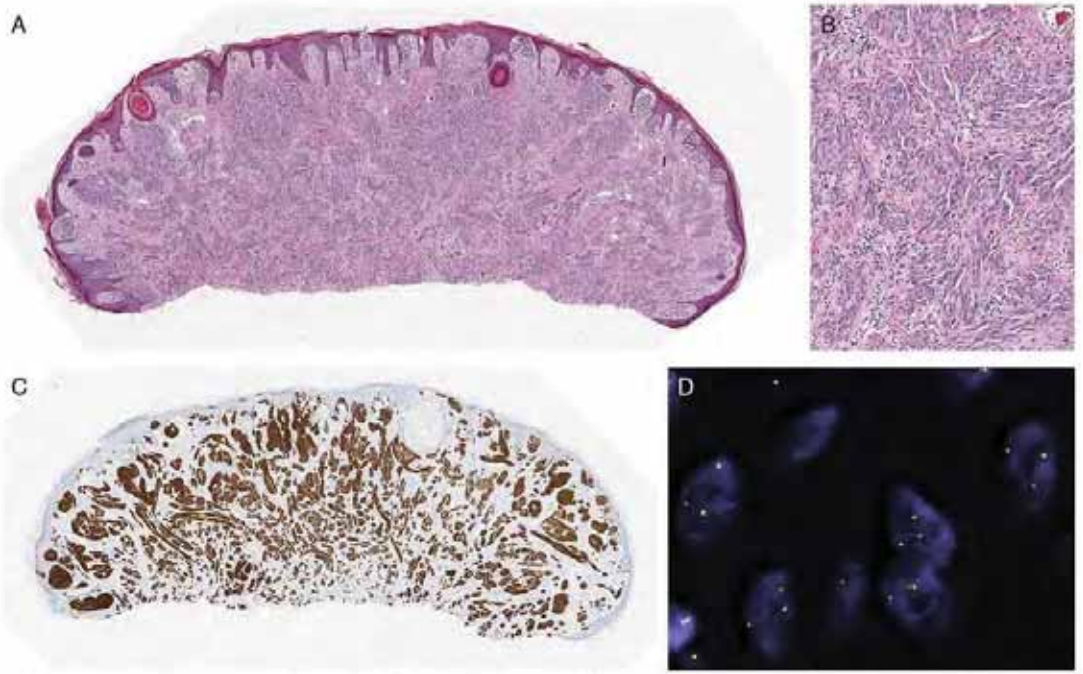

FIGURE 2. Spitz nevus with a *TPM3-ALK* fusion from the leg of a 25-year-old man (case 2). A, Silhouette of an amelanotic polypoid compound Spitz nevus (hematoxylin and eosin–stained section) with evidence of maturation. B, Proliferation of cytologically bland spindle and epithelioid melanocytes. C, The tumor cells are positive for ALK. D, FISH confirms the *ALK* rearrangements using break-point flanking probes by the individual green and red signals.

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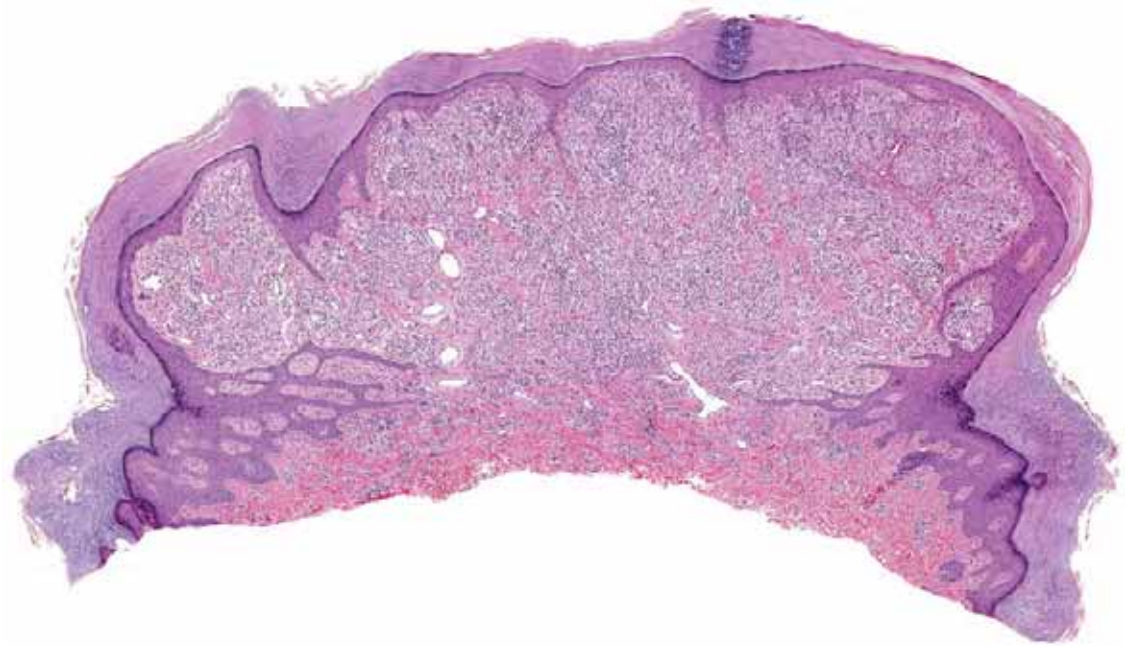

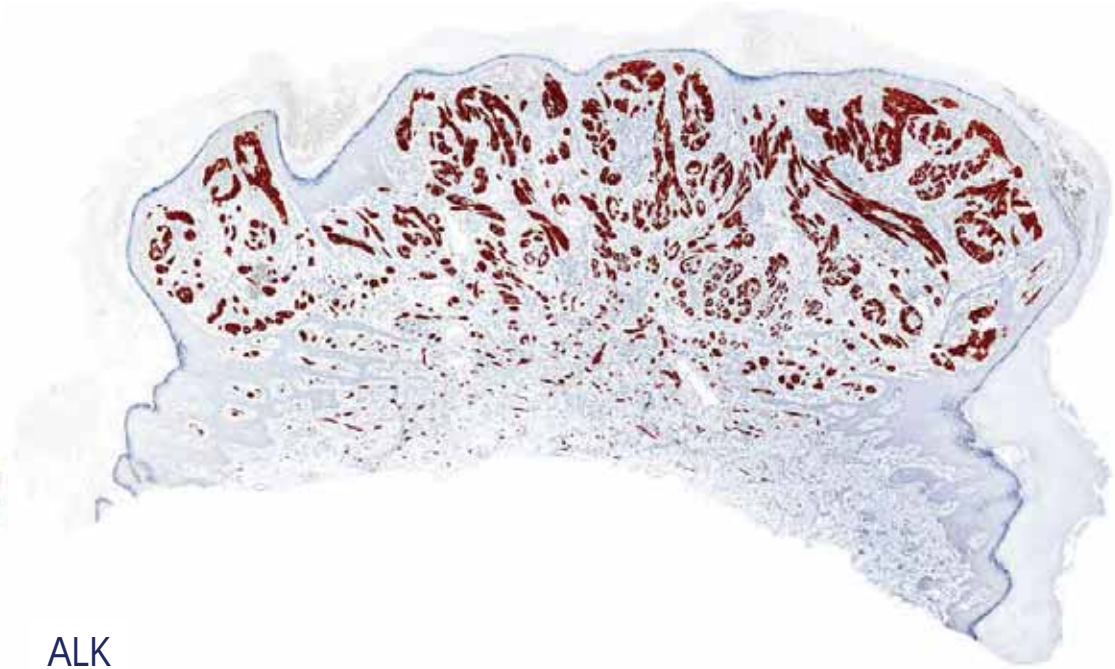

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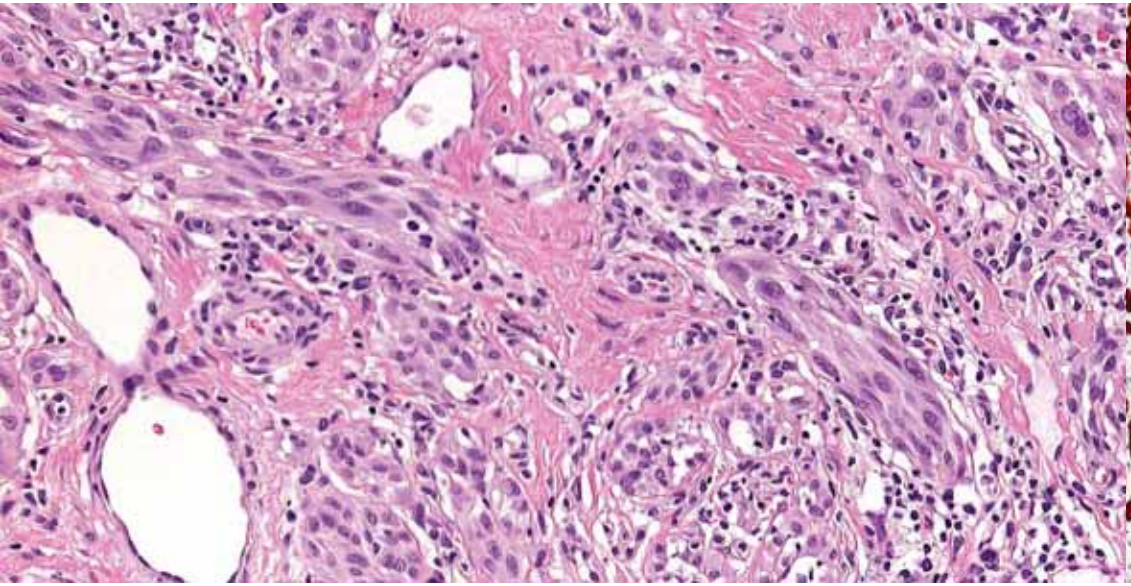

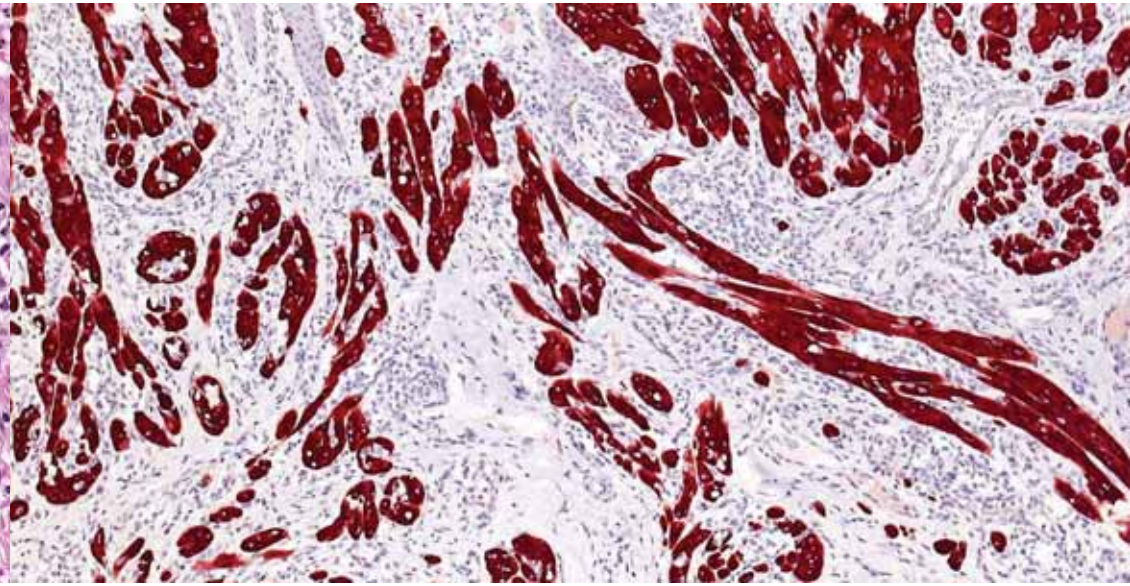

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ARTICLE

Clinical, morphologic, and genomic findings in *ROS1* fusion Spitz neoplasms

Pedram Gerami[1,2] · Daniel Kim[1] · Elsy V. Compres[1] · Bin Zhang[1] · Ayesha U. Khan[1] · Joel C. Sunshine[1] · Victor L. Quan[1] · Klaus Busam[3]

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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 ten Spitz nevi and seven 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 toward 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.

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 *ROS1* [1–16]. Genomic fusions involving the *ROS1* oncogene are seen in 7–17% of Spitz neoplasms [17, 18]. However, thus far only one study of six 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 (SN).

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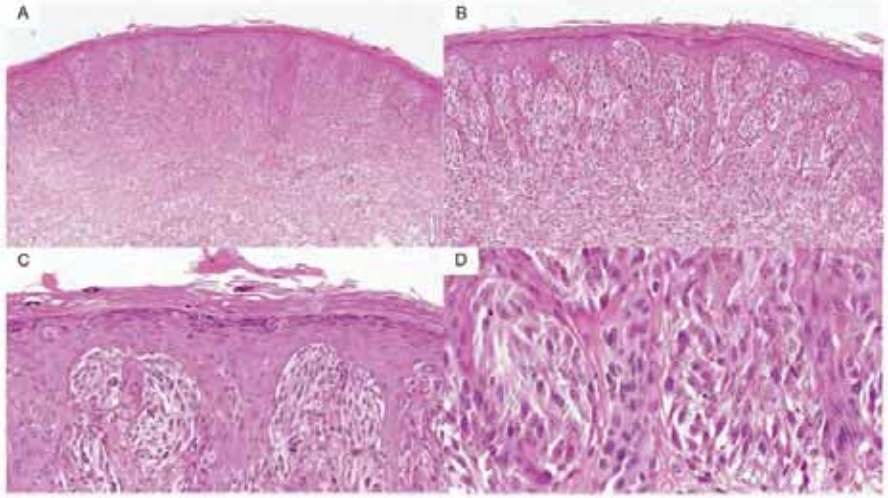

Fig. 1 Hematoxylin and Eosin staining on Case 1. a At 40× one can appreciate the plaque-like silhouette of this ROS1 fusion Atypical Spitz Tumor. **b** At 100× the epidermal hyperplasia with a predominance of nests with spindle-shaped melanocytes can be seen in a back-to-back pattern crowding the epidermis. **c** At 200× one can appreciate the transepidermal elimination of small nests into the stratum corneum. **d** 400× demonstrates the Spitzoid cytomorphology with relatively low-grade nuclear atypia.

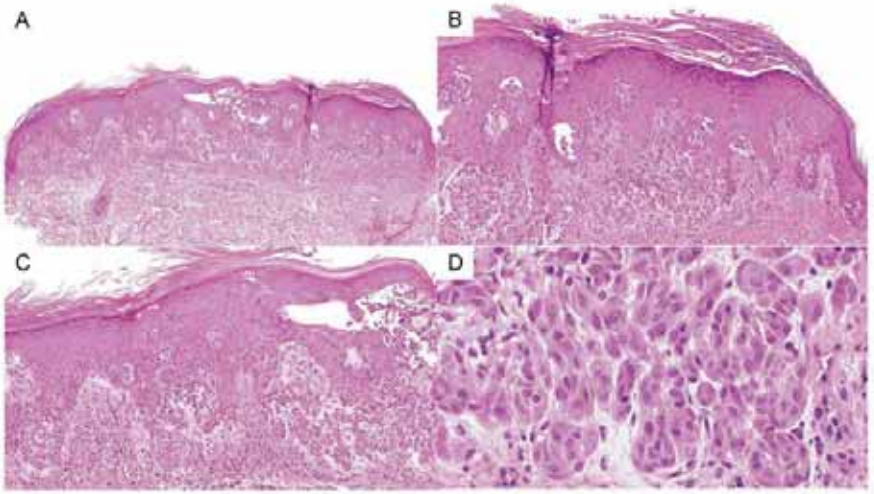

Fig. 2 Hematoxylin and Eosin staining on Case 2. a, b At 40× and 100×, respectively, a plaque-like Atypical Spitz Tumor with epidermal hyperplasia and back-to-back expansile nests. **c** At 200× one can appreciate some floating nests in the epidermis. **d** At 400× one can appreciate the relatively bland cytology of the Spitzoid melanocytes.

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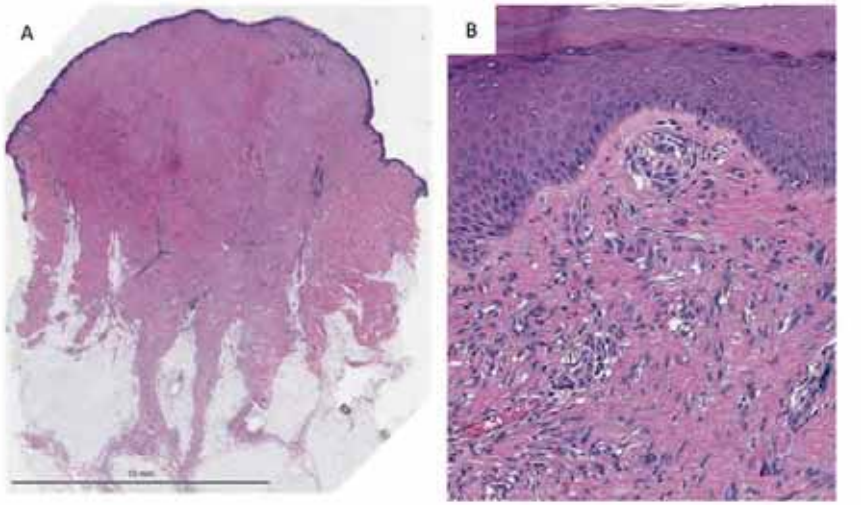


Fig. 3 Hematoxylin and Eosin staining on Case 13. a Low power shows a symmetric paucicellular Spitzoid neoplasm in a desmoplastic stroma. **b** Higher magnification shows small nests and individual units of Spitzoid melanocytes entrapped in a sclerotic stroma consistent with a diagnosis of desmoplastic Spitz nevus.

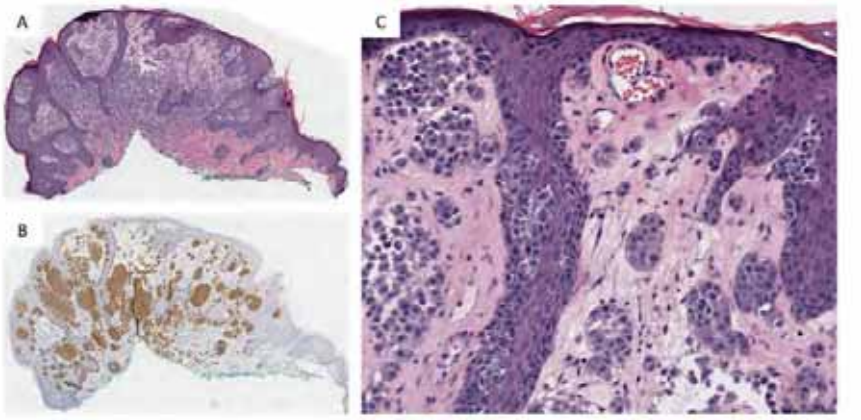
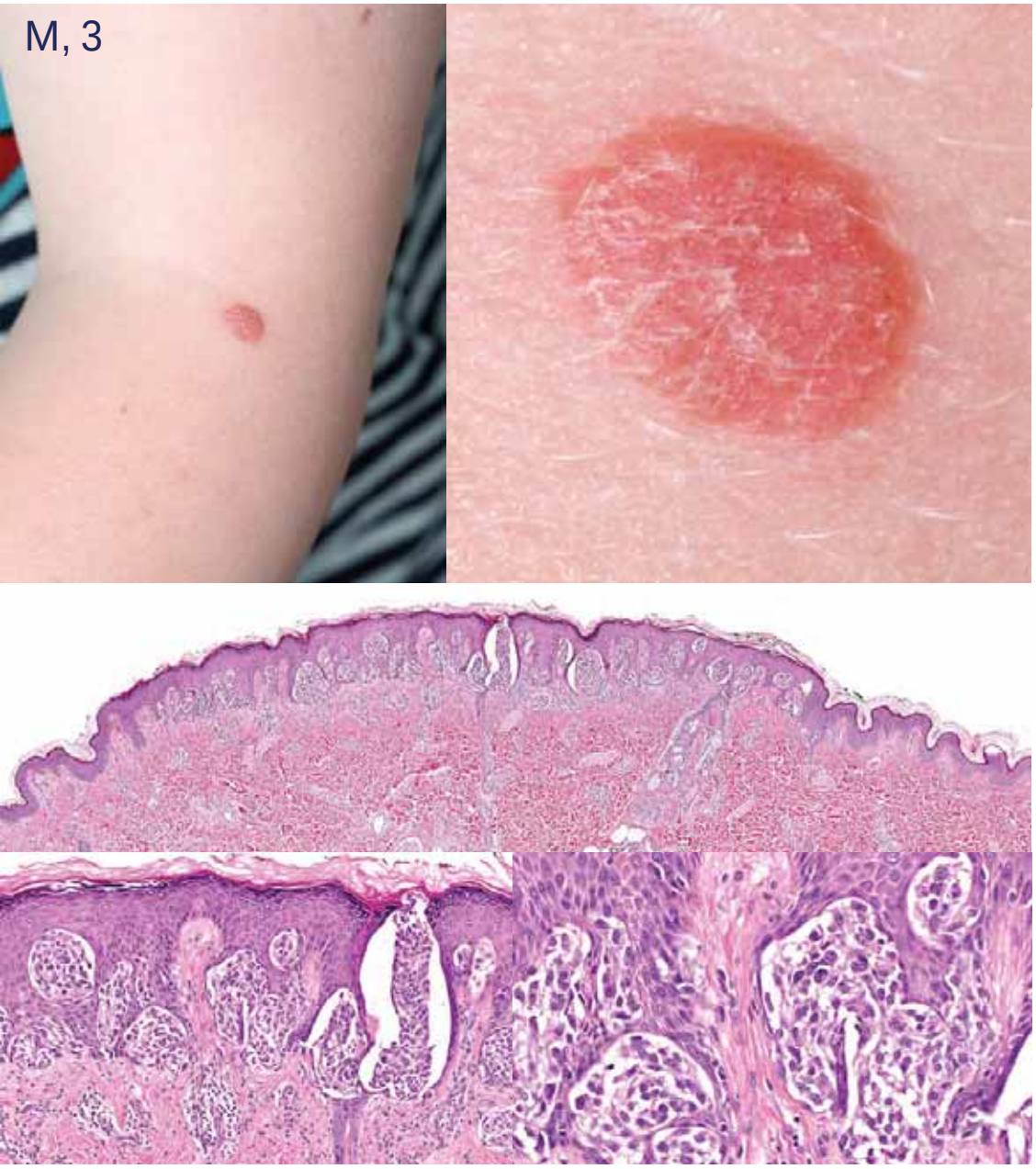


Fig. 4 An example of a strong positive IHC staining for ROS1. a Low power showing plaque-like silhouette of a ROS1 Fusion Spitz nevus. **b** IHC staining for ROS1 shows strong and uniform staining throughout the nevus. **c** Higher magnification shows nests of epithelioid and spindle-shaped melanocytes with bland cytomorphology lacking significant atypia.

Spitz naevus subtypes (WHO 5th edition, *beta version*)

Specific molecular anomalies, particularly fusion genes in the MAP kinase pathway, appear to have a correlation with various histological patterns. However, it is important to note that multiple histological patterns may occur within the same tumour, and this may not necessarily indicate an exclusive genetic alteration.

Genetic features	*Histological patterns*	*Clinical subtypes*
ALK fusions	Plexiform with elongated fascicles of spindle cells, myxoid, angiomatoid. Often high mitotic counts and may have ulceration.	
ROS1 fusions	Plexiform or plaque like, angiomatoid. Highly characteristic features is floating nests in the epidermis with transepidermal elimination of nests and are often frequently pagetoid.	
NTRK1 fusions	Filigree-like rete ridges, exaggerated maturation, often pigmented and predominantly spindle cell morphology are common, lobulated nesting pattern, rosettes, dysplastic naevus-like appearance.	
NTRK3 fusions	Early lesions appear dysplastic, more evolved lesions have variable pattern according to 5' fusion partners (neuroid, desmoplastic).	
BRAF fusions	Hyalinizing, dysplastic, often predominantly epithelioid.	
HRAS mutations	Desmoplastic.	Eruptive
PRKAR1α-inactivation as secondary event	Pigmented epithelioid cell.	
MYO5A fusions mainly *MYO5A::NTRK3*	Neuroid.	
MAP3K8	Predominantly epithelioid and often highly pleomorphic, sometimes pigmented.	
RET fusions	Plaque-type, sometimes with dyscohesive nesting.	



The dogmas of the WHO classification

The "Spitz lineage" is restricted to some molecular features including several kinase fusions (an expanding spectrum) and mutations of *HRAS*, but does not include cases with mutations of *BRAF* or *NRAS*.

Like all melanocytic tumors, tumors of the Spitz lineage, too, progress through a benign, an intermediate, and a malignant stage.

What makes a melanocytic tumor a "Spitz tumor" ?

Is it morphology ?
Is it history (i.e., what was called "Spitz" in the last decades ?)
Is it genetic ?
Is it a combination of these features ?

At present:

Morphology + tyrosine kinase fusions (various) = Spitz
Morphology + serine-threonine kinase fusions (various) = Spitz
Morphology + mutations (i.e., *HRAS*) = Spitz
Morphology + mutations (e.g., *BRAF*) ≠ Spitz

Morphology + "non-Spitz lineage" molecular features ≠ Spitz

nature genetics

Germline mutations in *BAP1* predispose to melanocytic tumors

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Common acquired melanocytic nevi are benign neoplasms that are composed of small, uniform melanocytes and are typically present as flat or slightly elevated pigmented lesions on the skin. We describe two families with a new autosomal dominant syndrome characterized by multiple, skin-colored, elevated melanocytic tumors. In contrast to common acquired nevi, the melanocytic neoplasms in affected family members ranged histopathologically from epithelioid nevi to atypical melanocytic proliferations that showed overlapping features with melanoma. Some affected individuals developed uveal or cutaneous melanomas. Segregating with this phenotype, we found inactivating germline mutations of *BAP1*, which encodes a ubiquitin carboxy-terminal hydrolase. The majority of melanocytic neoplasms lost the remaining wild-type allele of *BAP1* by various somatic alterations. In addition, we found *BAP1* mutations in a subset of sporadic melanocytic neoplasms showing histological similarities to the familial tumors. These findings suggest that loss of *BAP1* is associated with a clinically and morphologically distinct type of melanocytic neoplasm.

We report a type of melanocytic neoplasm that was inherited in an autosomal dominant pattern in two unrelated families and that was clinically, histopathologically and genetically distinct from common acquired nevi (**Fig. 1a**). Beginning in the second decade of life, affected family members progressively developed skin-colored to reddish-brown, dome-shaped to pedunculated, well-circumscribed papules with an average size of 5 mm (**Fig. 1b** and **Supplementary Figs. 1–4**). The number of tumors per individual varied markedly, ranging from 5 to over 50. No intellectual disabilities or dysmorphic features were identified in affected individuals.

Histopathological examination identified primarily dermal tumors composed entirely or predominantly of epithelioid melanocytes with abundant amphophilic cytoplasm and prominent nucleoli. The melanocytes often contained large, vesicular nuclei that varied substantially in size and shape (**Fig. 1c** and **Supplementary Figs. 5–7**). The cytological features of some of the cells were reminiscent of Spitz nevi; however, characteristic features (such as epidermal hyperplasia, hypergranulosis, Kamino bodies, clefting around junctional melanocytic nests and spindle-shaped melanocytes) frequently seen in Spitz nevi were consistently absent. In addition, 37 of 42 (88%) tumors in the families showed mutations in the *BRAF* proto-oncogene, which are typically absent in Spitz nevi[1].

Some of the neoplasms showed one or more atypical features such as high cellularity, considerable nuclear pleomorphism and several chromosomal aberrations. These tumors were classified as 'neoplasms of uncertain malignant potential', and the affected individuals were managed as if they had melanoma (**Supplementary Fig. 8**). Both families were identified because of the occurrence of multiple epithelioid melanocytic tumors, but, in each family, one affected individual had uveal melanoma, and three members of family 2 had been diagnosed with cutaneous melanoma (**Fig. 1a** and **Supplementary Table 1**).

We analyzed 22 melanocytic neoplasms from three affected individuals (II-1, II-4 and II-7) in family 1 by array-based comparative genomic hybridization (aCGH). We found losses affecting the entire chromosome 3 or portions of the short arm of chromosome 3 in 50% of tumors. The smallest overlap of the deleted regions encompassed 5.8 Mb, extending from position 47,976,758 to 53,848,761 (hg 18 assembly) and encoded at least 150 known genes (**Fig. 2a**).

The frequent loss of the 3p21 region suggested a second hit[2] resulting in the elimination of the remaining wild-type allele of a mutated tumor suppressor gene in this region. To support this hypothesis,

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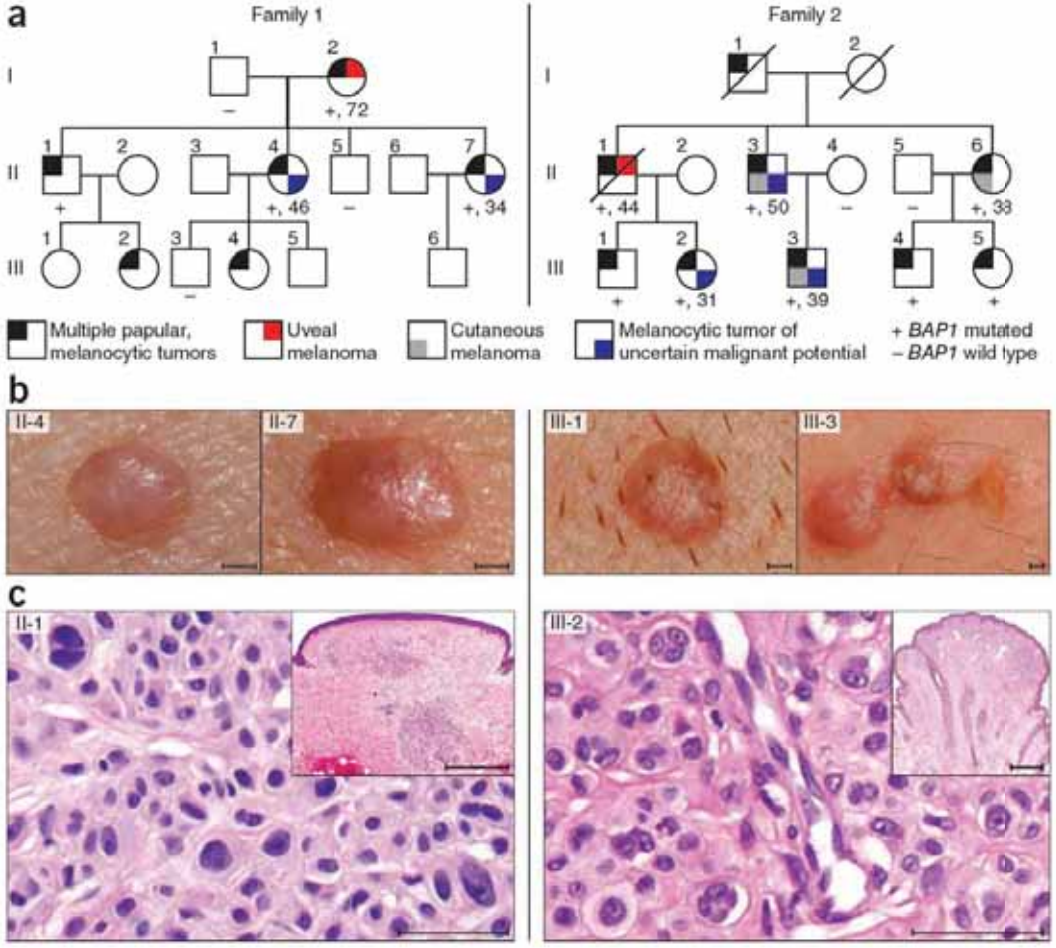
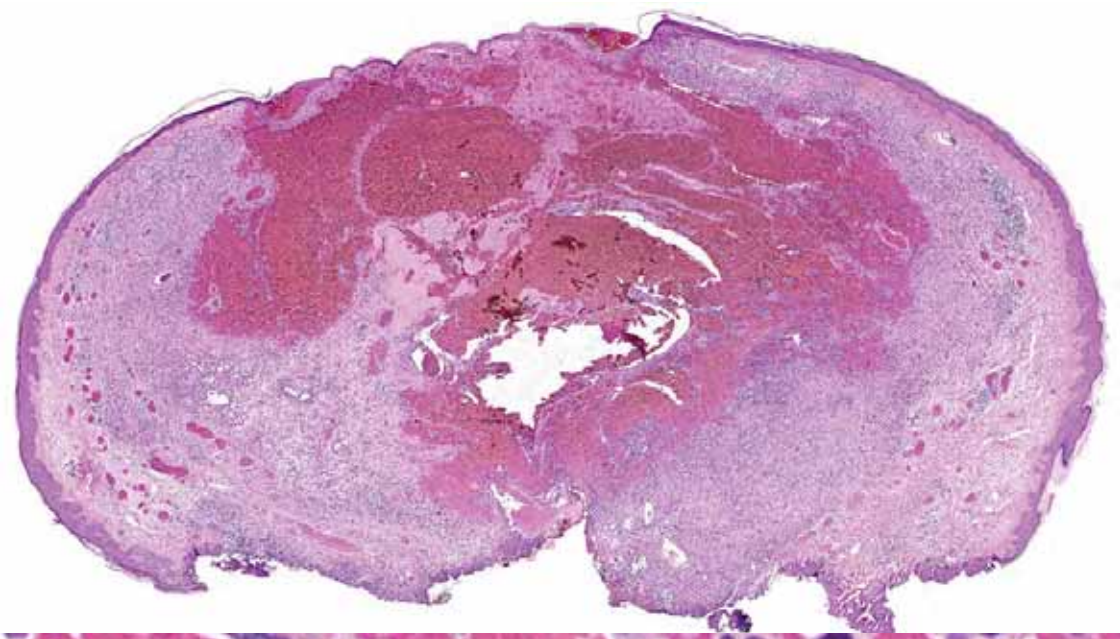
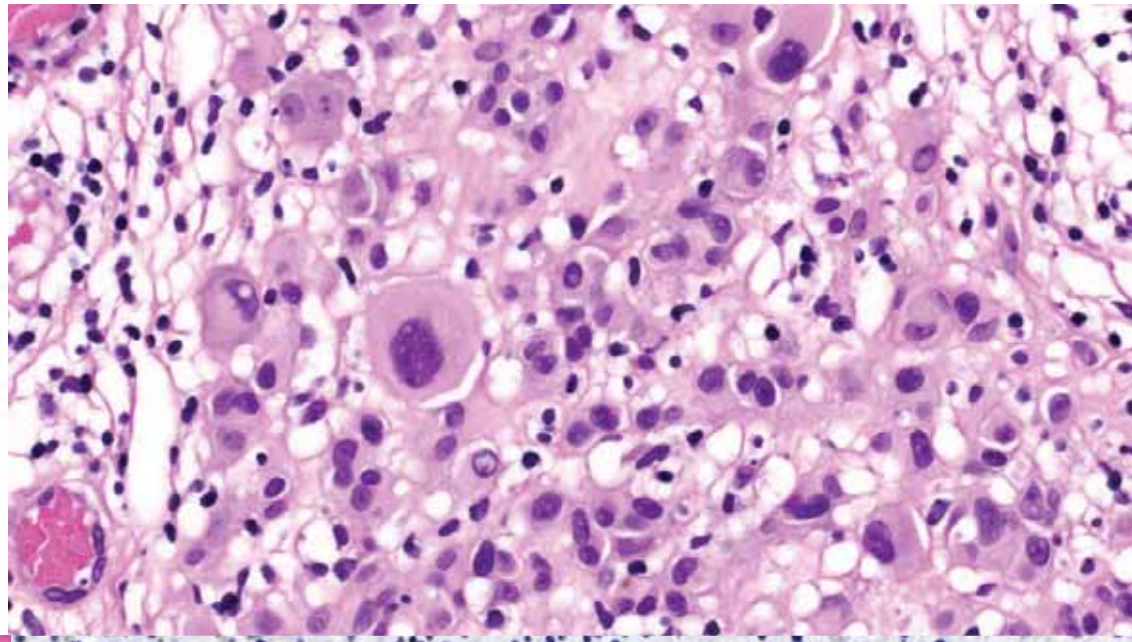
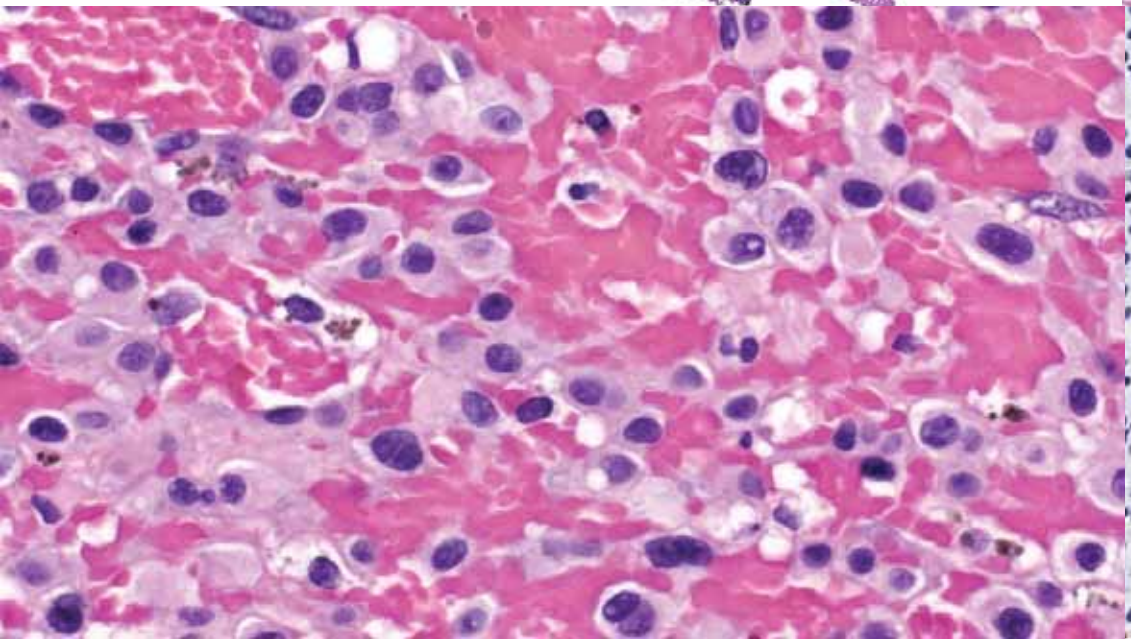
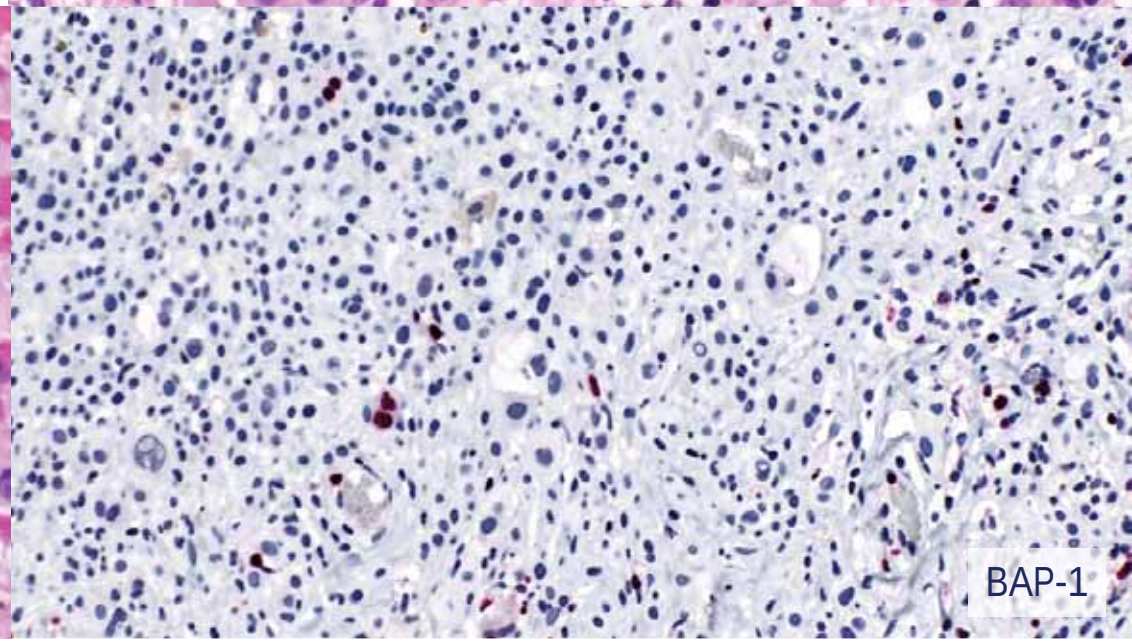


Somatic *BAP1* mutation in 3/60 sporadic MMs from patients without family history of melanocytic neoplasms (1 acral MM, 2 MM on non chronic sun-damaged skin).








BAP-1

	Sun-exposed skin with low or moderate CSD				Sun-exposed skin with high CSD		Tumours not caused by UV radiation					
Pathway	I				II	III	IV	V	VI	VII	VIII	IX
Endpoint of pathway	Low-CSD melanoma (including SSM)				High-CSD melanoma / LMM	Desmoplastic melanoma	Malignant Spitz tumour /Spitz melanoma	Acral lentiginous melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN	Uveal melanoma
Benign neoplasms (naevi)		Naevus			? IMP	? IMP	Spitz naevus	Field cells (field effect) [c]	? Melanosis	CN	Blue naevus	? Uveal naevus
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIM	WNT-activated deep penetrating/ plexiform melanocytoma (naevus)		? IAMP / dysplasia	? IAMP / dysplasia	Spitz melanocytoma (Atyipical Spitz Tumour)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	BAP1-inactivated melanocytoma / MELTUMP	WNT-activated deep penetrating/plexiform melanocytoma (naevus) / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS	STUMP / MELTUMP	Acral lentiginous MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant neoplasms	Low-CSD melanoma including SSM	Melanoma in BIM	Melanoma inWNT-activated deep penetrating/plexiform melanocytoma (naevus)	Melanoma in PEM	High-CSD melanoma / LMM	Desmoplastic melanoma	Malignant Spitz tumour/ Spitz melanoma (tumourigenic)	Acral lentiginous melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumourigenic)	Melanoma in blue naevus (tumourigenic)	Uveal melanoma
Common mutations[a,b] in addition to multiple DNA copy number changes found in the malignant stages of all melanoma subtypes	BRAF p.V600Eor NRAS	BRAF or NRAS + BAP1	BRAF, MAP2K1, or NRAS + CTNNB1 or APC	BRAF + PRKAR1A	NRAS; BRAF (non-p.V600E); KIT; or NF1	NF1; ERBB2; MAP2K1; MAP3K1; BRAF; EGFR; MET	HRAS; ALK; ROS1; RET; NTRK1; NTRK3; BRAF; RASGRF1; RASGRF2; MAP3K8, or MET	KIT; NRAS; BRAF; HRAS; KRAS; NTRK3; ALK; or NF1;SPRED1	KIT, NRAS, KRAS, or BRAF NF1; SPRED1	NRAS; BRAF p.V600E (small lesions); or BRAF	GNAQ, GNA11, CYSLTR2, PLCB4 or PRKCA	GNAQ, GNA11, CYSLTR2, or PLCB4
	TERT; CDKN2A; TP53;PTEN		TERT; CDKN2A; TP53;		TERT; CDKN2A; TP53; PTEN; RAC1	TERT; NRAS; PIK3CA; PTPN11	TERT; CDKN2A	CDKN2A; TERT; TERT CCND1; GAB2	CDKN2A; SF3B1; TERT; TERT; ATRX CCND1; CDK4; MDM2		BAP1; EIF1AX; SF3B1	BAP1; SF3B1; EIF1AX ; CENPE; TP53; RLP5

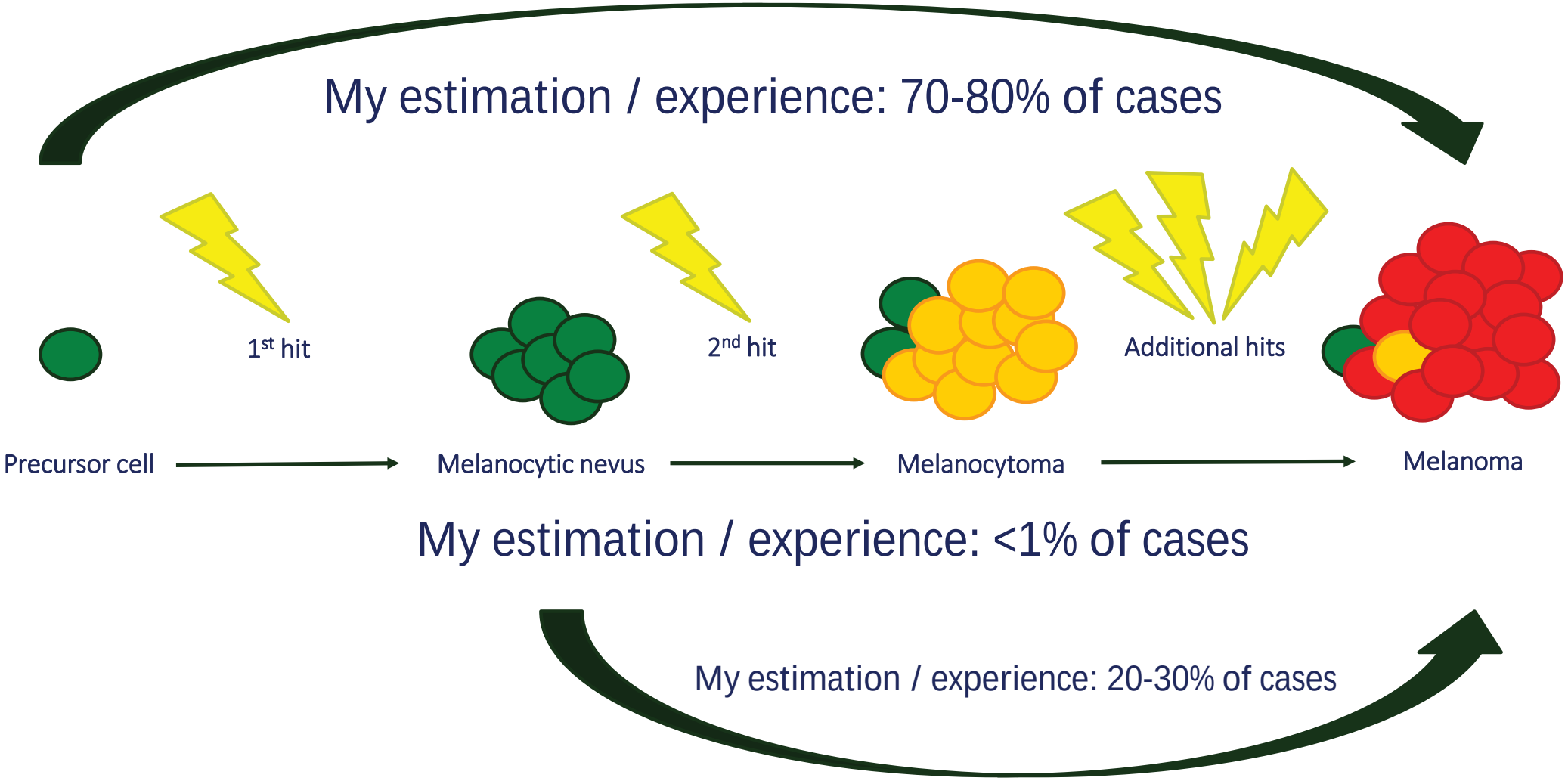
BIM, BAP1-inactivated melanocytoma; BN, blue naevus; CBN, cellular blue naevus; CN, congenital naevus; CSD, cumulative sun damage; IAMP, intraepidermal atypical melanocytic proliferation; IAMPUS, intraepidermal atypical melanocytic proliferation of uncertain significance; IMP, intraepidermal melanocytic proliferation without atypia; LMM, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; MELTUMP, melanocytic tumour of uncertain malignant potential; MIS, melanoma in situ; PEM, pigmented epithelioid melanocytoma; SSM, superficial spreading melanoma; STUMP, spitzoid tumour of uncertain malignant potential; UV, ultraviolet; VGP, vertical growth phase.

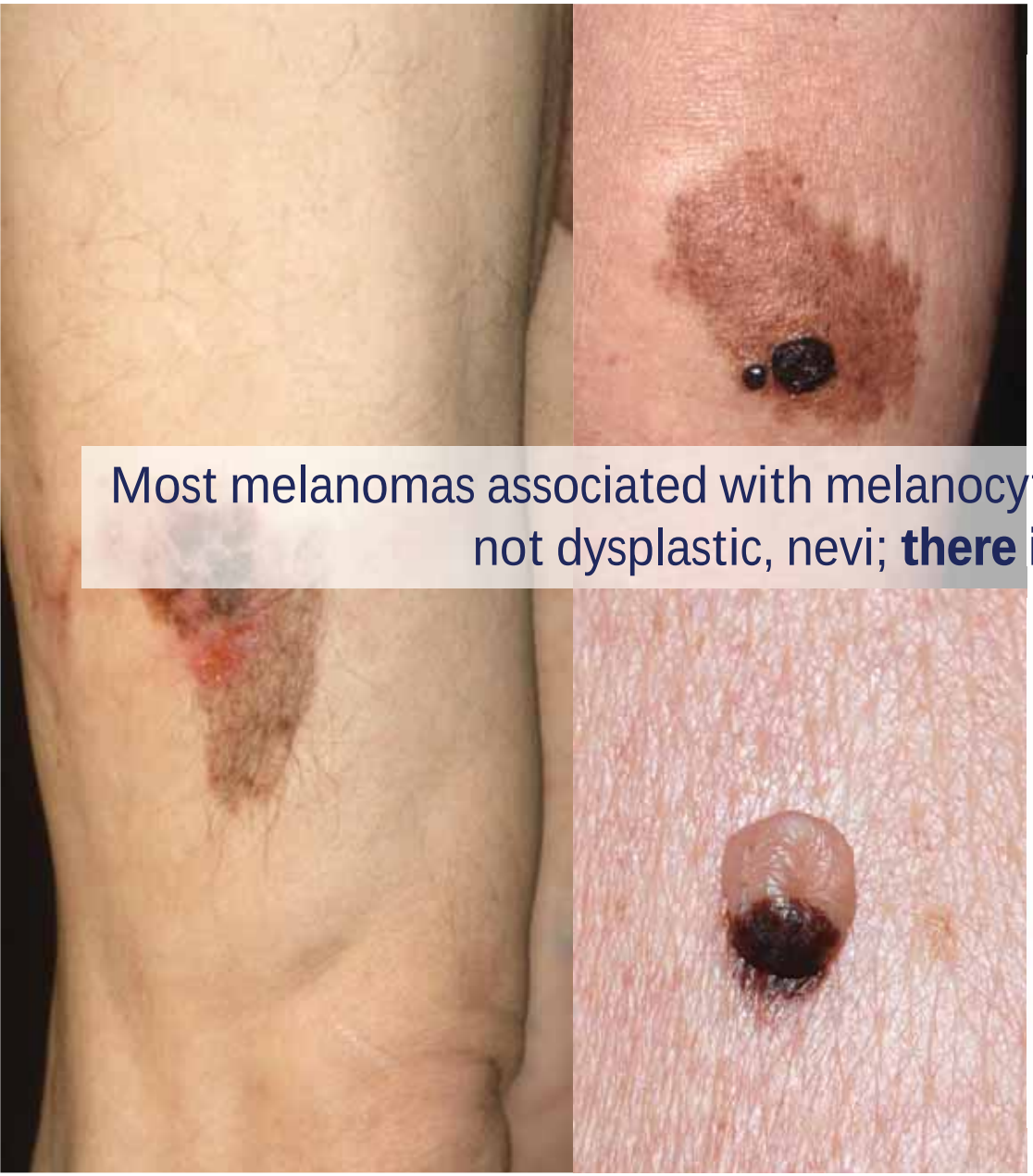
Definitions: Melanocytoma is a tumourigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia (compared with a common naevus) and an increased (although generally still low) probability of neoplastic progression; tumourigenic means forming a mass of neoplastic cells.

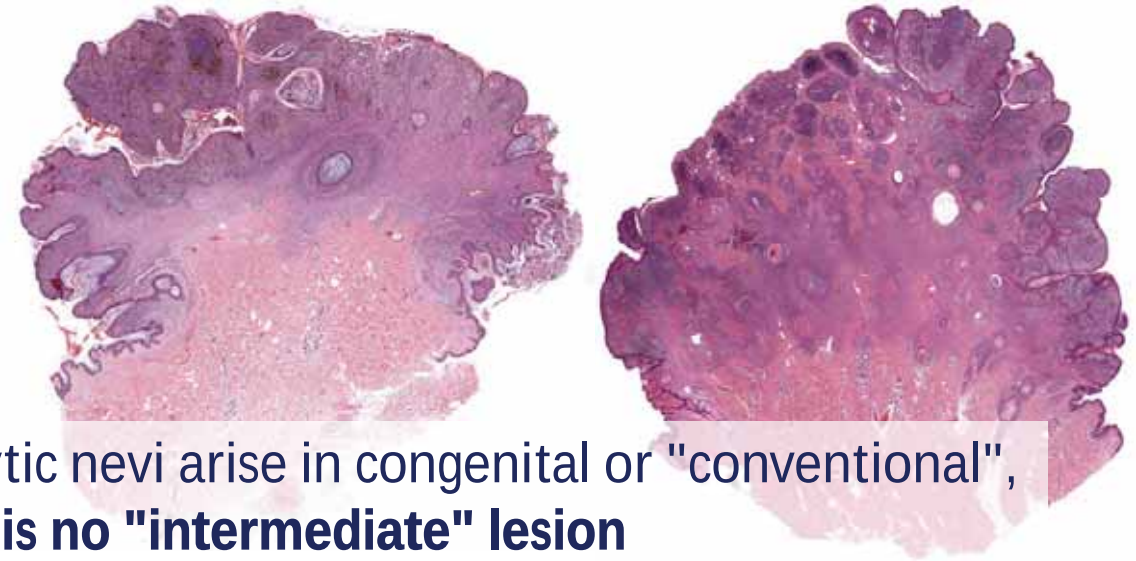
[a] Common mutations in each pathway are listed; mutations already identified in benign or borderline low lesions are shown in bold.
[b] Blue, loss-of-function mutation; red, gain-of-function mutation; green, change-of-function mutation; orange, amplification; purple, rearrangement; grey, promoter mutation.
[c] Basilar melanocytes with normal features or only slightly enlarged nuclei that share genetic alterations with an adjacent melanoma

CSD: cumulative sun damage; BIM: BAP-1 inactivated melanocytoma; PEM: pigmented epithelioid melanocytoma;
IMP: intraepidermal melanocytic proliferation without atypia; IAMP: intraepidermal atypical melanocytic proliferation

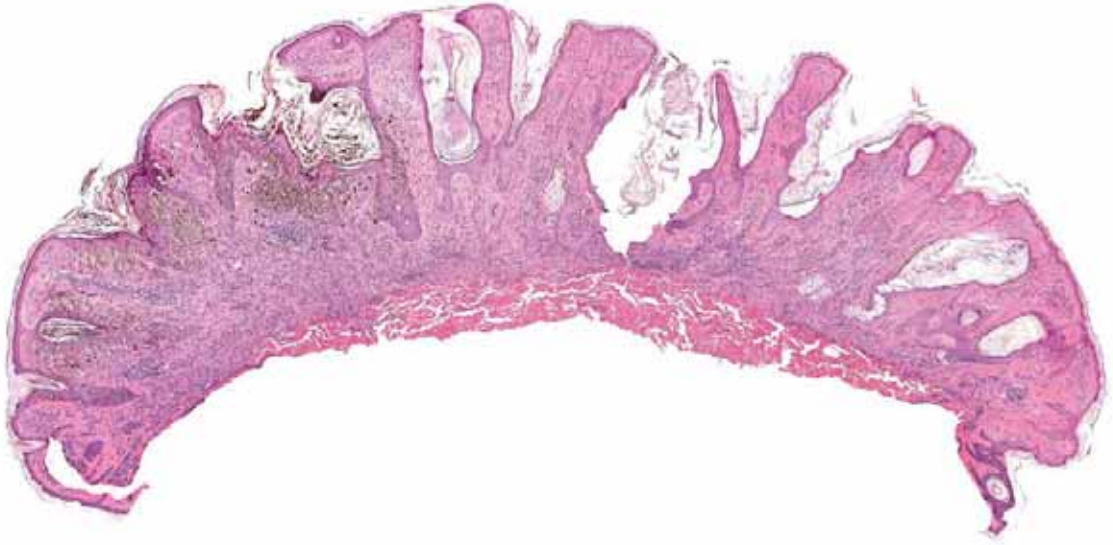
The evolution of melanoma from precursor cells

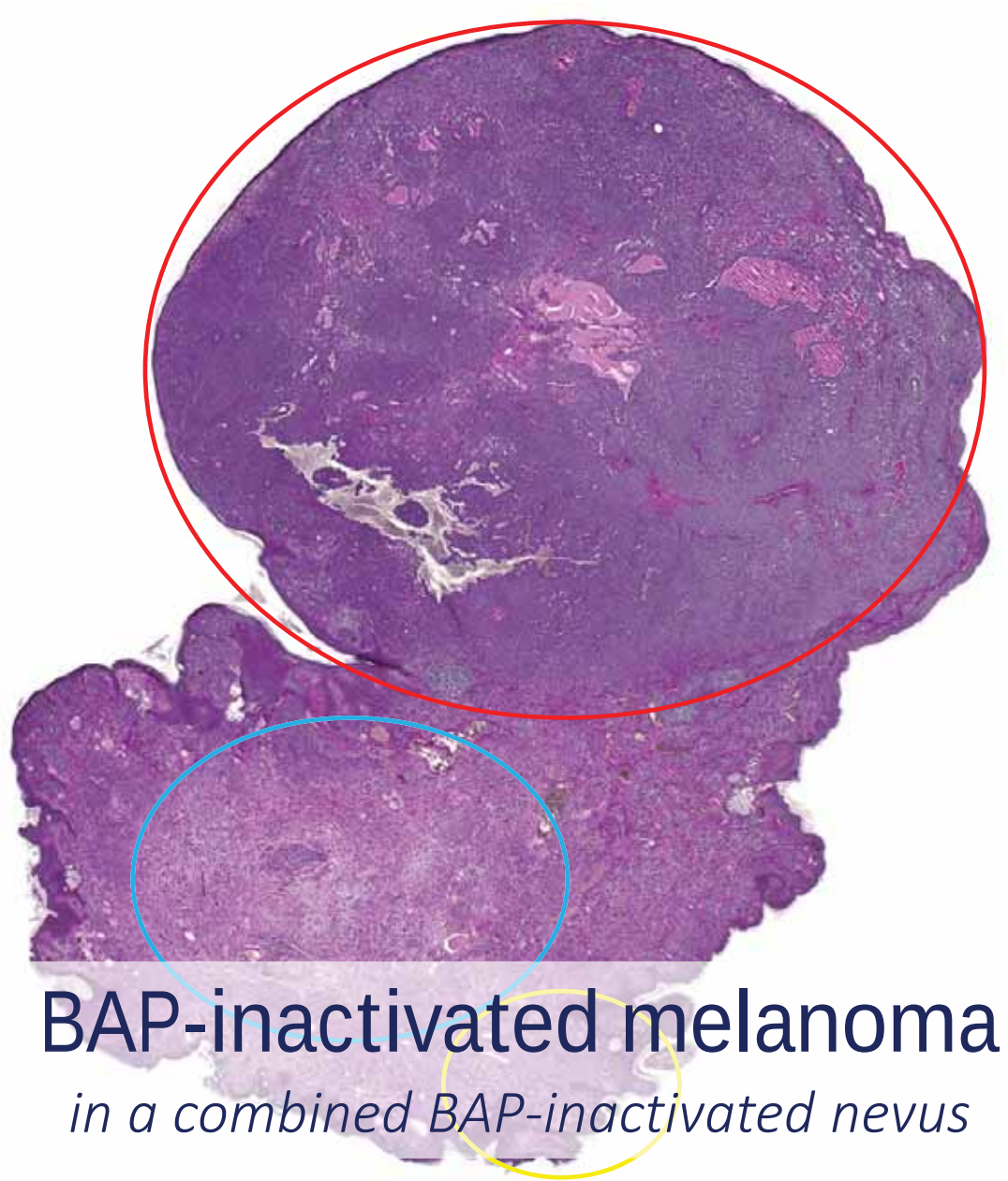






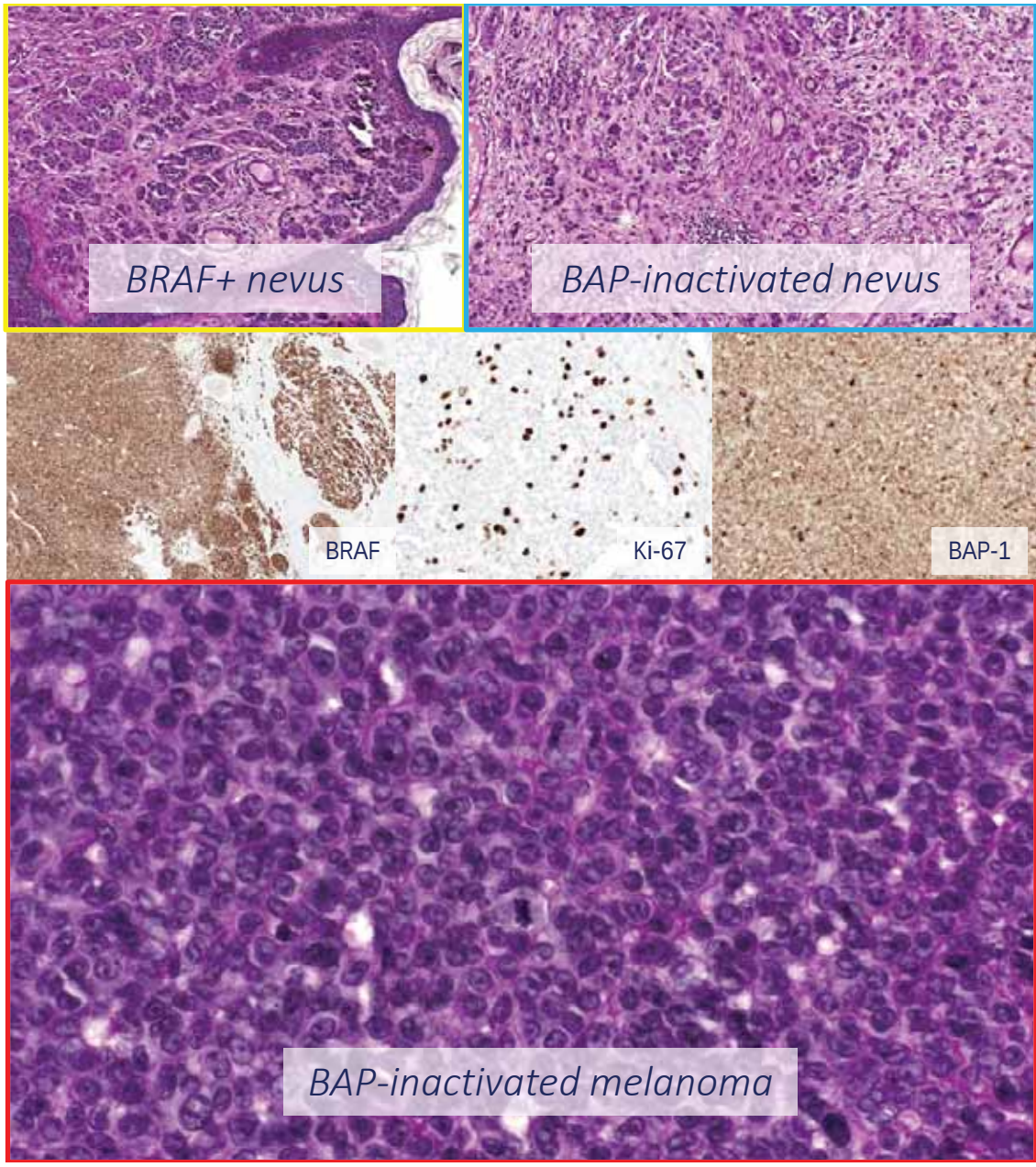
Most melanomas associated with melanocytic nevi arise in congenital or "conventional", not dysplastic, nevi; **there is no "intermediate" lesion**





BAP-inactivated melanoma

in a combined BAP-inactivated nevus



Spitz "lineage"

- *HRAS* mutations; tyrosine kinase fusions (*MET*, *ALK*, *ROS1, NTRK1, NTRK2, NTRK3*, *RET*, *MERTK, LCK*), serine-threonine kinase fusions (*MAP3K3*, *MAP3K8*, *BRAF*); (other molecular aberrations ?)
- Within each lineage: Spitz nevus, atypical Spitz tumor (Spitz melanocytoma), Spitz melanoma
- Differentiation of "Spitz nevus" from "Spitz melanocytoma (AST)" and from "Spitz melanoma (SM)" mostly morphological; number of molecular aberrations of AST and SM unknown
- WHO 5ed: "The distinction (of Spitz melanoma) from Spitz melanocytoma is best made by using a constellation of clinical, morphologic and molecular findings and no single data point can completely distinguish Spitz melanoma from Spitz melanocytoma."

MELANOCYTIC TUMOUR PATHOLOGY

An update on genomic aberrations in Spitz naevi and tumours

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Summary

Spitz neoplasms continue to be a diagnostic challenge for dermatopathologists and are defined by distinctive morphological and genetic features. With the recent advancements in genomic sequencing, the classification, diagnosis, and prognostication of these tumours have greatly improved. Several subtypes of Spitz neoplasms have been identified based on their specific genomic aberrations, which often correlate with distinctive morphologies and biological behaviour. These genetic driver events can be classified into four major groups, including: (1) mutations [HRAS mutations (with or without 11p amplification) and 6q23 deletions]; (2) tyrosine kinase fusions (ROS1, ALK, NTRK1-3, MET and RET); (3) serine/threonine kinase fusions and mutations (BRAF, MAP3K8, and MAP2K1); and (4) other rare genomic aberrations. These driver genomic events are hypothesised to enable the initial proliferation of melanocytes and are often accompanied by additional genomic aberrations that affect biological behaviour. The discovery of theses

melanocytic tumours diagnosed as a Spitz neoplasm resulting in aggressive clinical behaviour with metastasis and subsequent patient mortality. New molecular studies which have identified the primary genetic drivers of Spitz neoplasms as being predominantly the result of chimeric fusion kinases have provided an opportunity to go beyond morphology in diagnosing Spitz neoplasms.[1] The identification of a Spitz associated fusion kinase or alternatively a *HRAS* activating point mutation allows for a definitive classification of neoplasms into the Spitz family. Alternatively, the presence of *BRAF* or *NRAS* activating mutations or activating point mutations in other genes in the MAPKinase pathway known to be primary drivers of melanocytic tumours excludes these lesions from the Spitz family.[1]

Some of the Spitz associated kinase fusions have been associated with specific phenotypic patterns. Familiarity with these patterns can improve the accuracy and confidence of a diagnostician in designating a tumour in the Spitz family. Therefore, in thisreview, we will discuss some of the various morphological patterns that have been associated with spe-

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INTRODUCTION

Historically, the diagnosis of Spitz neoplasms has been one of the greatest challenges for pathologists. Many studies have documented the considerable lack of interobserver consensus in diagnosing Spitz neoplasms using only morphological criteria.[1] Further, there are many anecdotes that describe

erative of Spitzoid melanocytes (Fig. 1 demonstrating a common fusion). A subsequent study also identified *NTRK3* and *MAP3K8* as well as several other novel fusions as key drivers in Spitz neoplasms.[3] *MAP3K8* can develop a constitutively active kinase from a fusion event as described above or a truncation in which the 5′ regulatory is simply lost also results in constitutive activation of the 3′ kinase.[4–5] In this same study nearly 80% of Spitz neoplasms tested had either a kinase fusion or a constitutively activated kinase due to

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These findings highlight the utility of NGS in identifying *BRAF* or *NRAS* mutations to distinguish naevoid melanomas and other non-Spitz melanomas from Spitz neoplasms.

BRAF Mutated and Morphologically Spitzoid Tumors, a Subgroup of Melanocytic Neoplasms Difficult to Distinguish From True Spitz Neoplasms

Pedram Gerami, MD, Alice Chen, BA,* Natasha Sharma, MS,* Pragi Patel, BS,* Michael Hagstrom, BA,* Pranav Kancherla, HS,* Tara Geraminejad, HS,* Shantel Olivares, BA,* Asok Biswas, MD,† Marcus Bosenberg, MD, PhD,‡ Klaus J. Busam, MD,§ Arnaud de La Fouchardière, MD, PhD,‖ Lyn M. Duncan, MD,¶ David E. Elder, MBChB,# Jennifer Ko, MD, PhD,** Gilles Landman, MD,†† Alexander J. Lazar, MD, PhD,‡‡ Lori Lowe, MD,§§ Daniela Massi, MD, PhD,‖‖ Daniela Mihic-Probst, MD,¶¶ Douglas C. Parker, MD,## Richard A. Scolyer, MD,***†††‡‡‡ Christopher R. Shea, MD,§§§ Artur Zembowicz, MD, PhD,‖‖‖ Sook Jung Yun, MD, PhD,¶¶¶ Willeke A.M. Blokx, MD,### and Raymond L. Barnhill, MD*****

Abstract: Drivers of Spitz neoplasms include activating point mutations in *HRAS* and Spitz-associated genomic fusions. It has become evident that some *BRAF*-mutated melanocytic neoplasms can morphologically mimic Spitz tumors (STs). These have been termed *BRAF* mutated and morphologically spitzoid (BAMS). In this study, 17 experts from the International Melanoma Pathology Study Group assessed 54 cases which included 40 BAMS and 14 true STs. The participants reviewed the cases blinded to the genomic data and selected among several diagnostic options, including ST cases. There was poor interobserver agreement for the precise diagnosis of the BAMS (kappa = 0.16) but good agreement that these cases were not melanoma (kappa = 0.7). BAMS nevi/tumors can closely mimic Spitz neoplasms. Expert melanoma pathologists in this study favored a diagnosis of ST in nearly half of the BAMS cases. There are BAMS cases that even experts cannot morphologically distinguish from true Spitz neoplasms.

Key Words: melanoma, dysplastic nevi, Spitz nevi, atypical Spitz tumors, Spitz melanoma, BRAF

There is a group of benign and intermediate grade melanocytic spitzoid neoplasms with *BRAF* mutations that even expert pathologists cannot morphologically distinguish from true Spitz neoplasms.

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Key Words: melanoma, dysplastic nevi, Spitz nevi, atypical Spitz tumors, Spitz melanoma, BRAF

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Genomics is rapidly being integrated into the diagnostic algorithm for challenging melanocytic neoplasms which may have histomorphological ambiguity.

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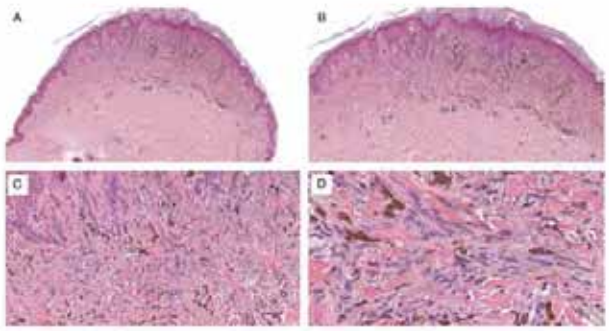

FIGURE 2. Case #39, BAMS. Low power magnification (A and B) shows a compound melanocytic neoplasm with overlying epidermal hyperplasia and a plaque-like silhouette from a 10-year-old. Higher power magnification (C and D) shows fascicles of spindle-shaped melanocytes with vesicular nuclei and abundant amphophilic pigmented cytoplasm (hematoxylin and eosin [H&E]).

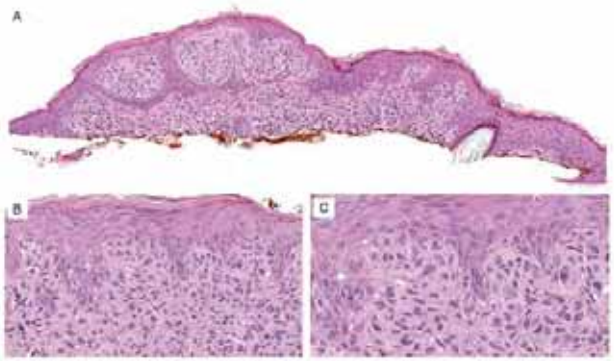

FIGURE 4. Case #4, BAMS. Low power magnification (A) shows a compound melanocytic neoplasm with overlying epidermal hyperplasia and epithelioid melanocytes with spitzoid cytomorphology from an 8-year-old. Higher power magnification (B and C) demonstrates cells with vesicular nuclei and abundant eosinophilic cytoplasm (H&E).

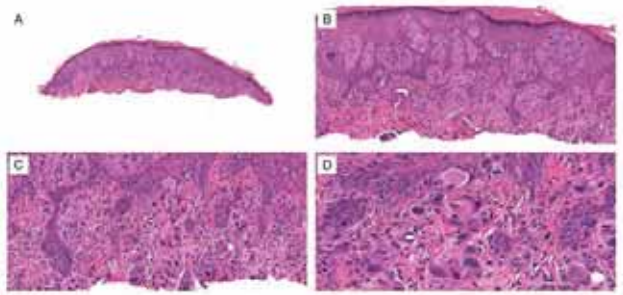

FIGURE 3. Case #13, BAMS. Low power magnification (A and B) demonstrates a compound spitzoid melanocytic neoplasm with overlying epidermal hyperplasia from a 12-year-old. Higher power magnification (C and D) shows prototypical spitzoid morphology with many of the cells having vesicular nuclei prominent nucleoli and abundant glassy eosinophilic cytoplasm (H&E).

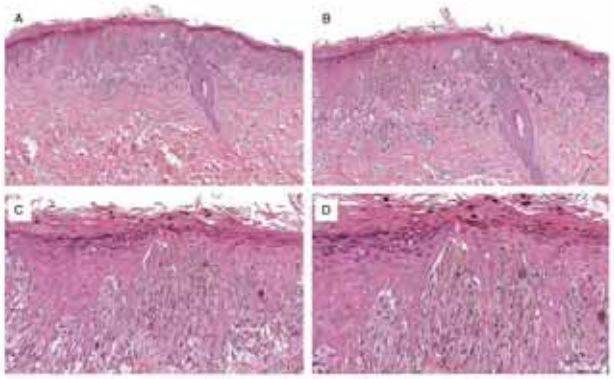

FIGURE 5. Case #10, a MAP3K8 fusion atypical ST. Low power magnification (A and B) demonstrates a compound but predominantly intraepidermal, well-nested, and circumscribed melanocytic proliferation with overlying epidermal hyperplasia. On higher power magnification (C), there are clefting spaces between the hyperplastic epidermis and the junctional melanocytic nests. At the highest magnification (D), the cells have vesicular nuclei and abundant cytoplasm which is granular and pigmented to slightly vacuolated appearing (H&E).

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Research Article

Amplification of Mutant *NRAS* in Melanocytic Tumors With Features of Spitz Tumors

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ABSTRACT

NRAS activating mutations are prevalent in melanocytic neoplasia, occurring in a subset of common acquired melanocytic nevi and ~30% of cutaneous melanomas. In this study, we described a cohort of 7 distinctive melanocytic tumors characterized by activating point mutations in codon 61 of *NRAS* with amplification of the mutant *NRAS* allele and shared clinicopathologic features. These tumors occurred predominantly in younger patients, with a median age of 20 years (range, 6-56 years). They presented as papules on the helix of the ear (4 cases) or extremities (3 cases). Microscopically, the tumors were cellular, relatively well-circumscribed, compound, or intradermal proliferations. The tumor cells often extended into the deep reticular dermis and involved the superficial subcutaneous fat in some cases. The melanocytes were epithelioid to spindled with moderate amounts of cytoplasm and conspicuous nucleoli. They were arranged in short plexiform fascicles, nests, and cords. Some cases had occasional pleomorphic and multinucleated melanocytes. Rare dermal mitotic figures were present in all cases. The dermis contained thick collagen bundles and minimal solar elastosis. Follow-up data were available for 5 patients, with a median period of 4.2 years (range, 1-9 years), during which no recurrences or metastases were reported. Our series highlights a clinicopathologically and molecularly distinctive subset of *NRAS* mutated tumors with amplification of the mutant *NRAS* allele.

Introduction

Progression in melanocytic neoplasia is mediated by the stepwise accumulation of genetic alterations.[1,2] The *WHO Classification of Skin Tumours* currently recognizes 9 evolutionary pathways to melanoma development.[3,4] In several pathways, benign, intermediate, and malignant tumors have been identified corresponding to melanocytic nevus, melanocytoma, and melanoma, respectively. The distinct types of melanocytic nevi within different pathways include common acquired melanocytic nevi, blue nevi, and Spitz nevi.

The common acquired melanocytic nevus belongs to the low–cumulative sun damage (CSD) pathway and typically harbors activating BRAF V600E mutations and less commonly contains activating mutations in NRAS instead.[5-8] Sequencing and copy

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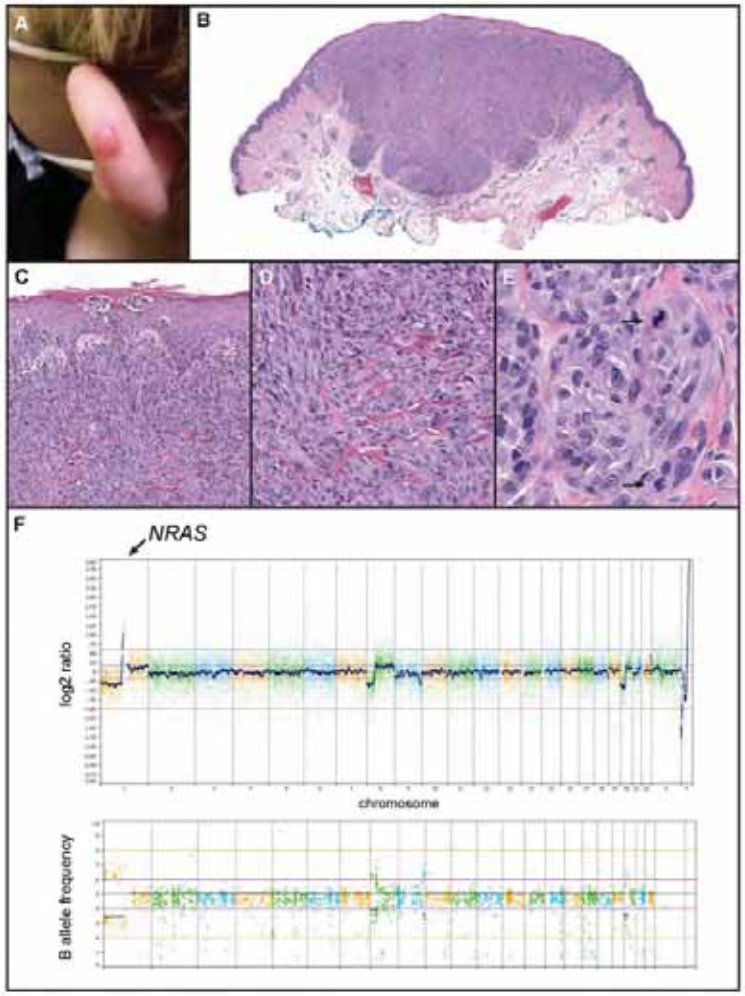

Figure 1.
Clinicopathologic and molecular findings of case 1. (A) The lesion presented as a skin-colored papule on the helix. (B) Low-power image showing a symmetrical, wedge-shaped compound tumor with a bulbous base and extension to the subcutis. (C) There were scattered pagetoid nests and single melanocytes within the hyperplastic epidermis. (C, D) The melanocytes were relatively monotonous and arranged in plexiform fascicles, cords, and nests. The dermis was sclerotic. (E) Rare dermal mitotic figures were present. (F) Copy number and B allele frequency plots showing *NRAS* amplification and segmental losses of distal 1p, 8p, distal 9q, and 20p loss.

Impact of Next-generation Sequencing on Interobserver Agreement and Diagnosis of Spitzoid Neoplasms

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Abstract: Atypical Spitzoid melanocytic tumors are diagnostically challenging. Many studies have suggested various genomic markers to improve classification and prognostication. We aimed to assess whether next-generation sequencing studies using the Tempus xO assay assessing mutations in 1711 cancer-related genes and performing whole transcriptome mRNA sequencing for structural alterations could improve diagnostic agreement and accuracy in assessing neoplasms with Spitzoid histologic features. Twenty expert pathologists were asked to review 70 consultation level cases with Spitzoid features, once with limited clinical information and again with additional genomic information. There was an improvement in overall agreement with additional genomic information. Most significantly, there was increase in agreement of the diagnosis of conventional melanoma from moderate ($\kappa = 0.470$, SE = 0.0105) to substantial ($\kappa = 0.645$, SE = 0.0143) as measured by an average Cohen κ. Clinical follow-up

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S.B. and J.Z. contributed equally to this article.

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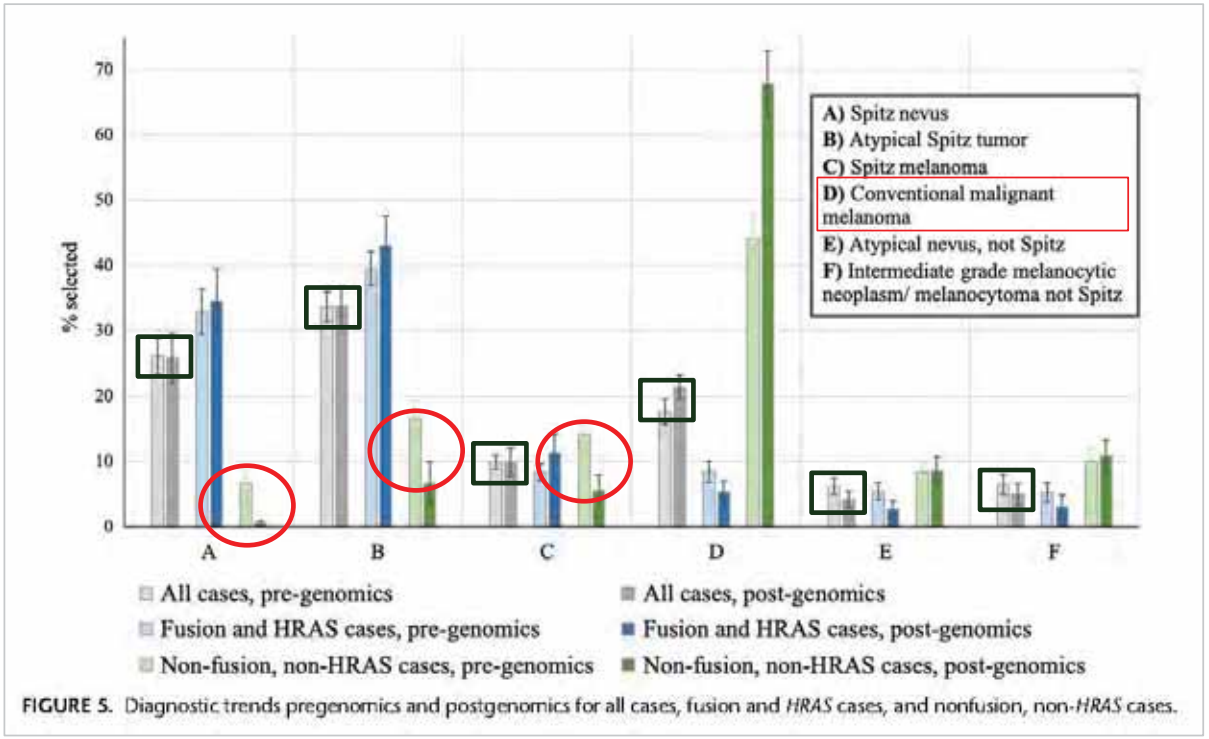

FIGURE 5. Diagnostic trends pregenomics and postgenomics for all cases, fusion and *HRAS* cases, and nonfusion, non-*HRAS* cases.

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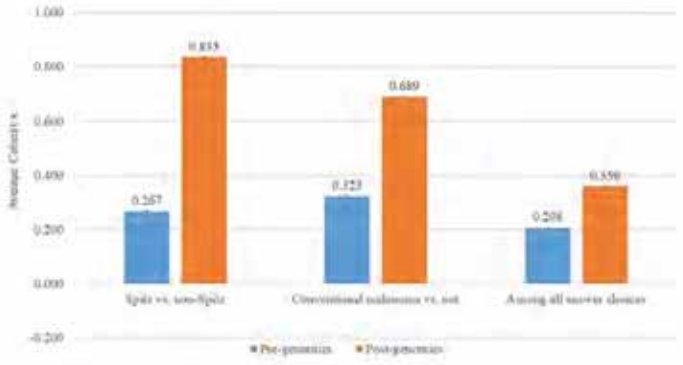
ORIGINAL ARTICLE

WILEY

Next-generation sequencing improves agreement and accuracy in the diagnosis of Spitz and spitzoid melanocytic lesions

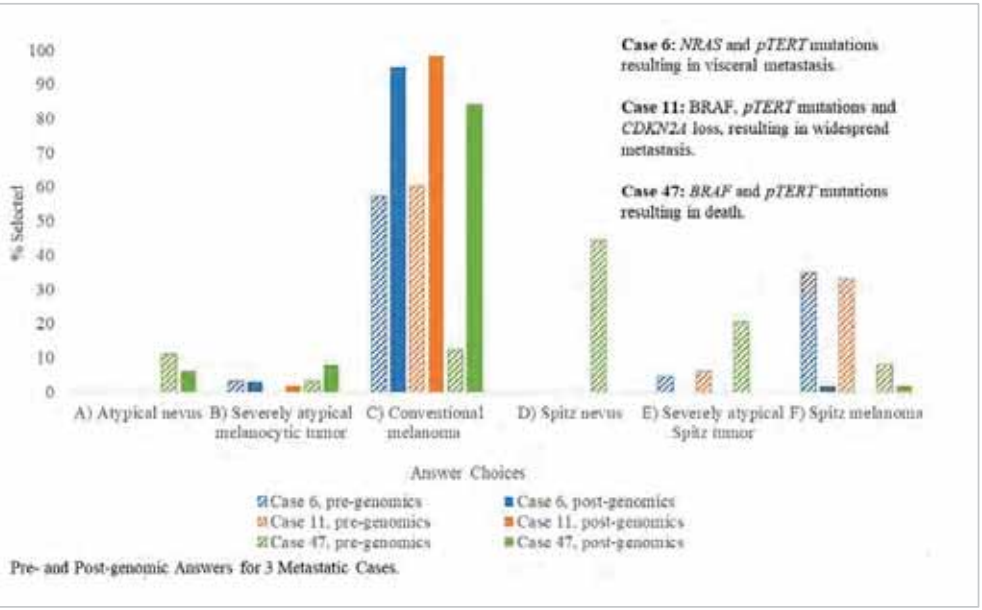
Andrew Roth BS[1] | Nathaniel Lampley 3rd BS[1] | Anastasiya Boutko MS[1] | Jeffrey Zhao BA[1] | Sarah Benton BA[1] | Shantel Olivares BA[1] | Artur Zembowicz MD, PhD[2] | Pedram Gerami MD[1,3]

63 "non-expert" dermatopathologists and general pathologists;
70 cases of melanocytic neoplasms with spitzoid features.

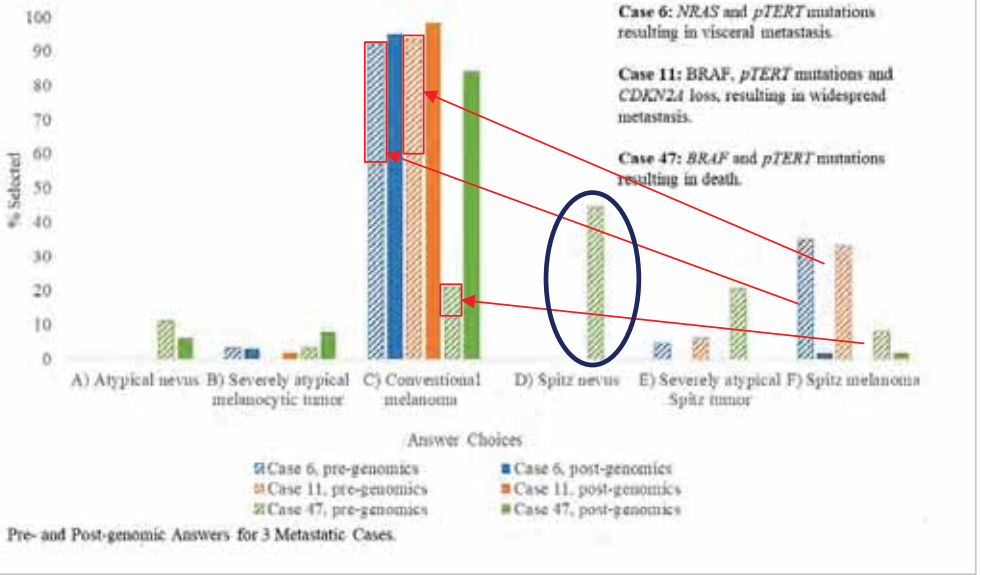


Inter-Rater Agreement for 3 Categories.

FIGURE 1 Diagnostic agreement for pre- and post-genomics for all 70 cases as measured by the average Cohen's κ for Spitz versus non-Spitz, conventional melanoma versus not, and among all answer choices



Pre- and Post-genomic Answers for 3 Metastatic Cases.



Pre- and Post-genomic Answers for 3 Metastatic Cases.

The FEBS Journal

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REVIEW ARTICLE

A recent update on small-molecule kinase inhibitors for targeted cancer therapy and their therapeutic insights from mass spectrometry-based proteomic analysis

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Keywords
cancer; kinase inhibitor; kinobeads; phosphoproteomics; thermal proteome profiling

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Kinases are key regulatory signalling proteins governing numerous essential biological processes and cellular functions. Dysregulation of many protein kinases is associated with cancer initiation and progression. Given their crucial roles, there has been increasing interest in harnessing kinases as prospective drug targets for cancer. In recent decades, numerous small-molecule kinase inhibitors have been developed and revolutionized the cancer treatment landscape. Despite their great potential, challenges remain in developing highly selective and effective kinase inhibitors, with toxicity and resistance issues frequently arising. In this review, we first provide an overview of the role of kinases in carcinogenesis and describe the current progress with small-molecule kinase inhibitors that have been approved for clinical use. We then discuss the application of mass spectrometry (MS)-based proteomics strategies to help in the design of kinase inhibitors. Finally, we discuss the challenges and outlook concerning MS-based proteomics techniques for kinase drug research.

Introduction

Kinases and their classification

During phosphorylation, a kinase catalyses the transfer of a phosphate group from an ATP to another specific substrate. Depending on the chemical properties of the substrates, kinases can be categorized into protein kinases, lipid kinases, carbohydrate kinases or even nucleoside-phosphate kinases or nucleoside-diphosphate kinases. For eukaryotic protein kinases, the main phosphorylatable sites are serine (Ser), threonine (Thr) and tyrosine (Tyr), whereas in prokaryotes, the main sites are aspartic acid (Asp), glutamic acid (Glu) and histidine (His) [1]. Other phosphorylatable amino acid residues include arginine (Arg), lysine (Lys) and cysteine (Cys) [2]. The human genome encodes ~ 518 kinase genes which

Abbreviations
ALK, anaplastic lymphoma kinase; ALL, acute lymphocytic leukaemia; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent kinase; CETSA, cellular thermal shift assay; CML, chronic myelogenous leukaemia; CSF1R, colony stimulating factor 1 receptor; DIA, data-independent acquisition; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3 receptor; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; JAK, Janus kinase; KI, kinase inhibitor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MS, mass spectrometry; mTOR, mechanistic target of rapamycin; NRY, non-receptor protein-tyrosine kinase; NSCLC, non-small cell lung cancer; PDGFR, platelet-derived growth factor beta-receptor; PI3K, phosphoinositide 3-kinases; PTM, post-translational modification; RCC, renal cell carcinoma; RET, rearranged during transfection; RTK, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; Syk, spleen tyrosine kinase; T/Y, dual specificity protein kinase; TKI, tyrosine kinase inhibitor; TPP, thermal proteome profiling; TRK, tropomyosin receptor kinases; VEGFR, vascular endothelial growth factor receptor.

Table 2. Summary of kinase inhibitors approved by FDA. NRY, non-receptor protein-tyrosine kinase; RTK, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; T/Y, dual-specificity protein kinase.

Drug	Brand	Manufacturer	Approved year	Target kinase	Target kinase family	Target disease: Non-cancer related disease	Target disease: Cancer	Type of kinase inhibitor
Abemaciclib	Verzenio	Eli Lilly and Company	2017	CDK4/6	S/T		Breast cancer	I
Acalabrutinib	Calquence	AstraZeneca	2017	BTK	NRY		Mantle cell lymphoma, chronic lymphocytic leukaemias, small lymphocytic lymphomas	I
Afatinib	Gilotrif, Tovok	Boehringer Ingelheim	2013	ErbB1/2/4	RTK		NSCLC (non-small cell lung cancer)	VI
Alectinib	Alecensa	Hoffmann-La Roche	2015	ALK, RET	RTK		ALK-positive NSCLC	I
Avapritinib	Ayvakit	Blueprint Medicines	2020	PDGFR	RTK		GIST (gastrointestinal stromal tumours)	I
Axitinib	Inlyta, AG013736	Pfizer	2012	VEGFR1/2/3	RTK		Advanced renal cell carcinoma	IIA
Baricitinib	Olumiant, LY3009104	Eli Lilly and Company	2018	JAK1/2	NRY	Rheumatoid arthritis		I
Belumosudil	Rezurock	Kadmon Pharmaceuticals, LLC	2021	ROCK2	S/T	Graft vs. host disease		I
Binimetinib	Mektovi, MEK162	Array Biopharma Inc.	2018	MEK1/2	T/Y		Melanoma	III
Bosutinib	Bosulif, SKI-606	PF Prism CV	2012	BCR-Abl	NRY		Chronic myelogenous leukaemias	IIB
Brigatinib	Alunbrig, AP26113	Takeda Pharms USA	2017	ALK	RTK		ALK-positive NSCLC	I
Cabozantinib	Cometriq, XL184, BMS907351	Exelixis	2012	RET, VEGFR2	RTK		Advanced medullary thyroid cancer, renal cell, and hepatocellular carcinoma	I
Capmatinib	INC280, Tabrecta	Novartis Pharm	2020	c-MET	RTK		NSCLC	I½B
Ceritinib	LDK378, Zykadia	Novartis	2014	ALK	RTK		ALK-positive NSCLC resistant to crizotinib	I
Cobimetinib	GDC-0973, Cotellic	Genentech Inc.	2015	MEK1/2	T/Y		BRAF mutation-positive melanoma in combination with vemurafenib	III
Crizotinib	Xalkori, PF-2341066	PF Prism CV	2011	ALK, ROS1	RTK		ALK or ROS1-positive NSCLC	I/I½B
Dabrafenib	Tafinlar, GSK2118436	Novartis	2013	B-Raf	S/T		BRAF mutation-positive melanomas, NSCLC and anaplastic thyroid cancers	II
Dacomitinib	PF-00299804, Vizimpro	Pfizer	2018	EGFR	RTK		EGFR-mutant NSCLC	VI
Dasatinib	BMS-354825, Sprycel	Bristol Myers Squibb	2006	BCR-Abl	NRY		Chronic myelogenous leukaemia	I/I½A
Encorafenib	LGX818, Braftovi	Array Biopharma Inc.	2018	B-Raf	S/T		Combination therapy for BRAFV600E/K melanoma	I
Entrectinib	RXDX-101, Ignyta, Rozlytrek	Genentech Inc.	2019	TRKA/B/C, ROS1	RTK		Solid tumours with NTRK fusion proteins, ROS1-positive NSCLC	I
Erdafitinib	JNJ-42756493, Balversa	Janssen Biotech	2019	FGFR1/2/3/4	RTK		Urothelial bladder cancers	I½
Erlotinib	OSI-774, Tarceva	OSI Pharms	2004	EGFR	RTK		NSCLC, pancreatic cancer	I/I½B
Everolimus	Rad001, Afinitor	Novartis	2009	FKBP12/mTOR	S/T		HER2-negative breast cancer, pancreatic neuroendocrine tumours, renal cell carcinoma, angiomyolipoma and subependymal giant cell astrocytoma	IV
Fedratinib	TG101348, Inrebic	Impact	2019	JAK2	NRY	Myelofibrosis		I
Fostamatinib	R788, Tavalisse	Rigel Pharms Inc.	2018	Syk	RTK	Chronic immune thrombocytopenia		I
Gefitinib	ZD1839, Iressa	AstraZeneca	2003	EGFR	RTK		NSCLC	I
Gilteritinib	ASP2215, Xospata	Astellas	2018	Flt3	RTK		Acute myelogenous leukaemia	I
Ibrutinib	PCI-32765, Imbruvica	Pharmacyclics Inc.	2013	BTK	NRY	Graft vs. host disease	Chronic lymphocytic leukaemia, mantle cell lymphoma, marginal zone lymphoma	VI

Table 2. (Continued).

Drug	Brand	Manufacturer	Approved year	Target kinase	Target kinase family	Target disease: Non-cancer related disease	Target disease: Cancer	Type of kinase inhibitor
Imatinib	STI571, Gleevec	Novartis	2001	BCR-Abl	NRY	Hypereosinophilic syndrome	Philadelphia chromosome-positive CML or ALL, aggressive systemic mastocytosis, chronic eosinophilic leukaemia, dermatofibrosarcoma protuberans, gastrointestinal stromal tumours, myelodysplastic/myeloproliferative disease	IIA
Infigratinib	BGJ-398, Truseltiq	QED Therapeutics, Inc.	2021	FGFRs	RTK		Cholangiocarcinomas with FGFR2 fusion proteins	I
Lapatinib	Tykerb	Novartis	2007	ErbB1/2/HER2	RTK		HER2-positive breast cancer	I/I½A
Larotrectinib	LOXO-101, Vitrakvi	Bayer Healthcare	2018	TRKA/B/C	RTK		Solid tumours with NTRK fusion proteins	
Lenvatinib	[illegible], Lenvima	Eisai Inc.	2015	VEGFR, RET	RTK		Differentiated thyroid cancer	I½A
Lorlatinib	PF-06463922, Lorbrena	Pfizer	2018	ALK	RTK		ALK-positive NSCLC	I
Midostaurin	CPG 41251, Rydapt	Novartis	2017	Flt3	RTK		Acute myelogenous leukaemia, mastocytosis, mast cell leukaemia	III
Mobocertinib	TAK-788, AP-32788, EXKIVITY	Takeda Pharmaceutical Company Limited	2021	EGFR with exon 20 insertions	RTK		NSCLC	VI
Neratinib	HKI-272, Nerlynx	Puma Biotech	2017	ErbB2/HER2	RTK		HER2-positive breast cancer	VI
Netarsudil	AR11324, Rhopressa	Aerie Pharms Inc.	2018	ROCK1/2	S/T	Glaucoma		I
Nilotinib	AMN107, Tasigna	Novartis	2007	BCR-Abl	NRY		Philadelphia chromosome-positive CML	IIA
Nintedanib	BIBF 1120, Ofev	Boehringer Ingelheim	2014	FGFR1/2/3	RTK	Idiopathic pulmonary fibrosis		IIB
Osimertinib	AZD-9292, Tagrisso	AstraZeneca	2015	EGFR T790M	RTK		NSCLC	VI
Palbociclib	Ibrance	Pfizer	2015	CDK4/6	S/T		Estrogen receptor-negative and HER2-positive breast cancer	I
Pazopanib	Votrient	Novartis	2009	VEGFR1/2/3	RTK		Renal cell carcinoma, soft tissue sarcomas	I
Pemigatinib	INCB054828, Pemazyre	Incyte Corp	2020	FGFR2	RTK		Cholangiocarcinoma with FGFR2 fusions or rearrangements	I
Pexidartinib	PLX3397, Turalio	Daiichi Sankyo Inc.	2019	CSF1R	RTK		Tenosynovial giant cell tumours	I
Ponatinib	Iclusig	Takeda Pharms USA	2012	BCR-Abl	NRY		Philadelphia chromosome-positive CML or ALL (acute lymphoblastic leukaemia)	I
Pralsetinib	BLU-667, Gavreto	Blueprint Medicines, Genentech Inc.	2020	RET	RTK		RET-fusion protein NSCLC	I
Regorafenib	Stivarga	Bayer Healthcare	2012	VEGFR1/2/3	RTK		Colorectal cancer, hepatocellular carcinoma	IIA
Ribociclib	LEE011, Kisqali	Novartis	2017	CDK4/6	S/T		Combination therapy for breast cancer	I
Ripretinib	DCC-2618, Qinlock	Deciphera Pharms	2020	KIT/PDGFR	RTK		GIST	II
Ruxolitinib	Jakafi	Incyte Corp	2011	JAK1/2/3, Tyk	NRY	Myelofibrosis, polycythemia vera		I
Selpercatinib	[illegible], Retevmo	Loxo Oncology Inc.	2020	RET	RTK		NSCLC, thyroid cancer	I
Selumetinib	AZD6244, Koselugo	AstraZeneca	2020	MEK1/2	T/Y		Neurofibromatosis type 1	I
Sirolimus	Rapamune	PF Prism CV	1999	FKBP12/mTOR	S/T	Kidney transplant	Lymphangioleiomyomatosis	IV
Sorafenib	Nexavar, BAY 43-9006	Bayer Healthcare	2005	VEGFR1/2/3	RTK		Hepatocellular carcinoma, renal cell carcinoma, thyroid cancer (differentiated)	IIA
Sunitinib	Sutent	CPPI CV	2006	VEGFR2	RTK		Gastrointestinal stromal tumours, renal cell carcinomas, pancreatic neuroendocrine tumours	I/IIA/IIB

Table 2. (Continued).

Drug	Brand	Manufacturer	Approved year	Target kinase	Target kinase family	Target disease: Non-cancer related disease	Target disease: Cancer	Type of kinase inhibitor
Temsirolimus	Torisel	PF Prism CV	2007	FKBP12/mTOR	S/T		Advanced renal cell carcinoma	IV
Tepotinib	Tepmetko	EMD Serono Inc.	2021	Met	RTK		Met mutant NSCLC	I
Tivozanib	Fotivda	Aveo Pharms	2021	VEGFR2	RTK		RCC	I
Tofacitinib	Xeljanz	PF Prism CV	2012	JAK3	NRY	Rheumatoid arthritis		I
Trametinib	Mekinist	Novartis	2013	MEK1/2	T/Y		Melanoma	III
Trilaciclib	Cosela	G1 Therapeutics	2021	CDK4/6	S/T	Myelosuppression		
Tucatinib	ONT-380, Tukysa	Seagen	2020	ErbB2/HER2	RTK		HER2-positive breast cancer	I
Upadacitinib	ABT-494, Rinvoq	Abbvie Inc.	2019	JAK1	NRY	Rheumatoid arthritis		I
Vandetanib	Caprelsa	Genzyme Corp.	2011	VEGFR2	RTK		Medullary thyroid cancer	I
Vemurafenib	Zelboraf	Hoffmann-La Roche	2011	B-Raf	S/T		BRAFV600E mutant melanoma	I½A
Zanubrutinib	BGB3111, Brukinsa	Beigene	2019	BTK	NRY		Mantle cell lymphoma	VI

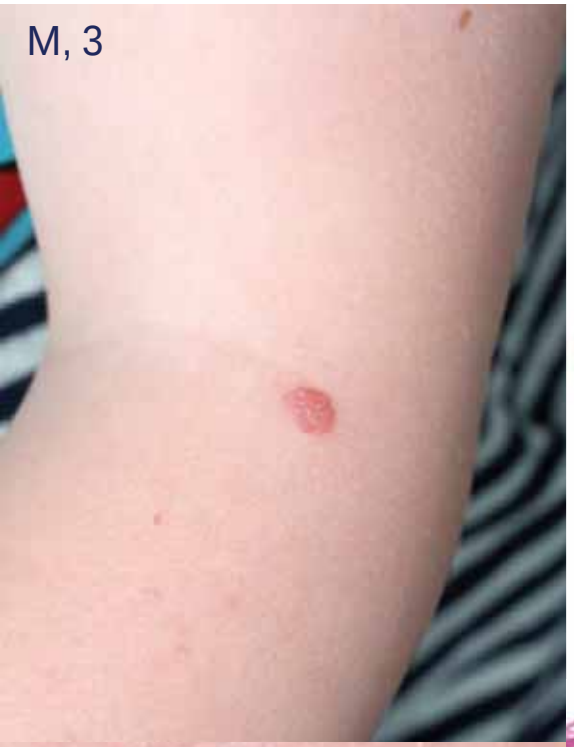
Current classification of "Spitz" lesions

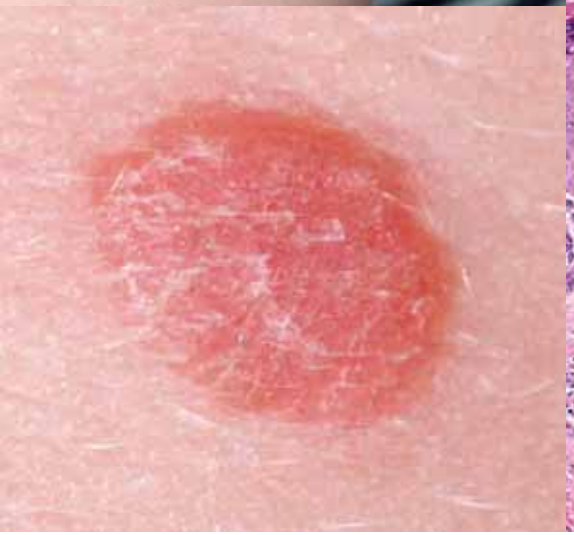
- **Spitz "lineage":** *HRAS* mutations; tyrosine kinase fusions (*MET*, *ALK*, *ROS1, NTRK1, NTRK2, NTRK3*, *RET*, *MERTK, LCK*), serine-threonine kinase fusions (*MAP3K3*, *MAP3K8*, *BRAF*); (other molecular aberrations; *BRAF* mutations ?)
- **Distinction of SN from AST and SM mostly morphological** (WHO: "AST usually have additional DNA alterations compared with SN.", *but one page later:* "The full spectrum of initiating mutations of Spitz tumours and the secondary alterations that distinguish AST from SN and melanomas remains to be characterized."
- **Spitz melanoma:** Spitz lineage initiating event; additional progression events (homozygous loss of *CDKN2A*, mutations in *TERT*, *CDK4*, *p53*, etc.); spread beyond local lymph nodes, but prognosis seems better than classic melanoma

For what is worth

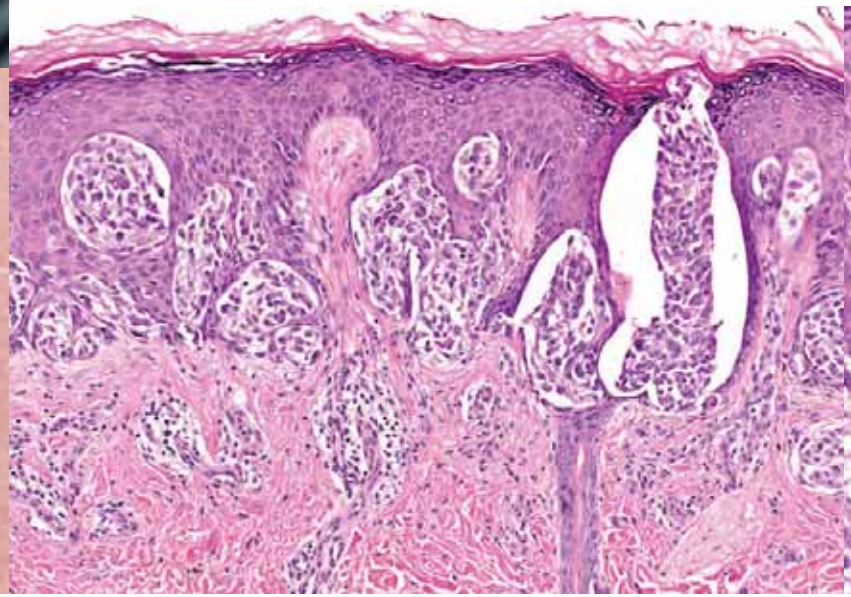
My personal approach
to "spitzoid" tumors
by conventional dermatopathology

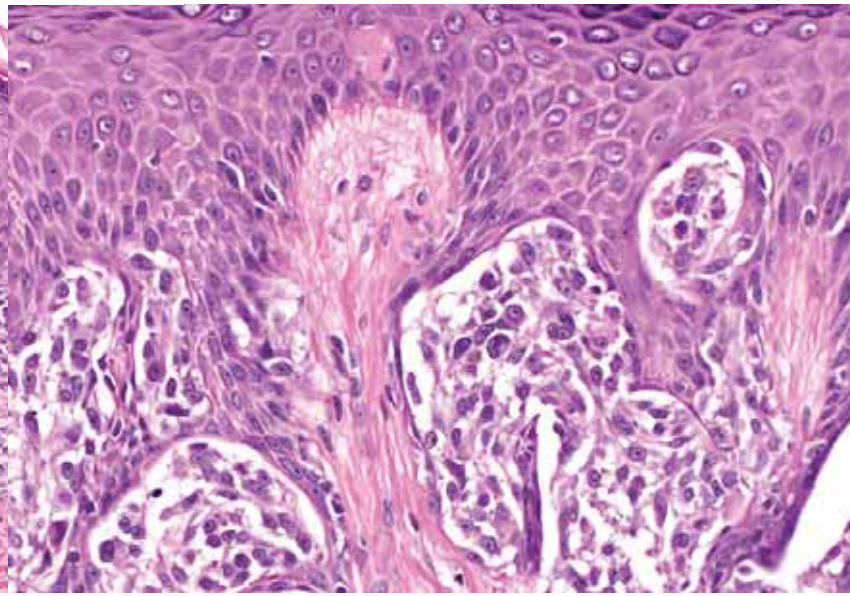
M, 3

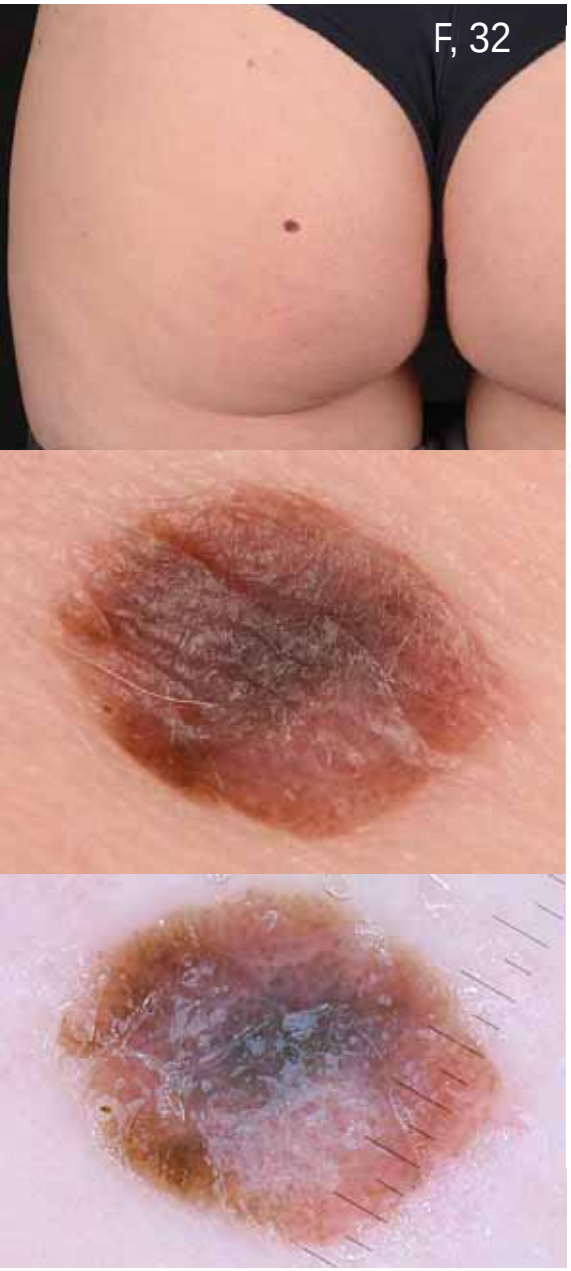


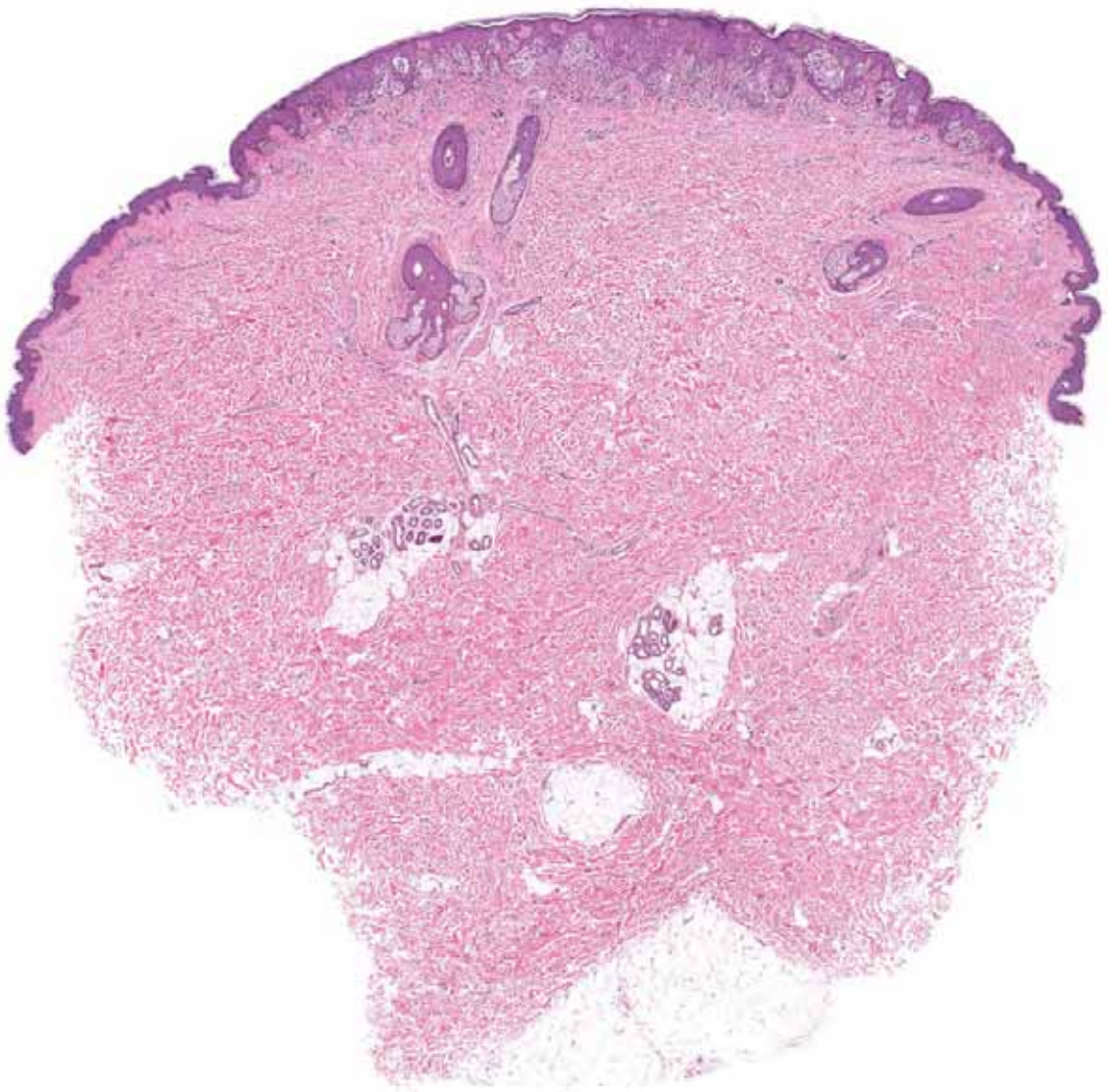


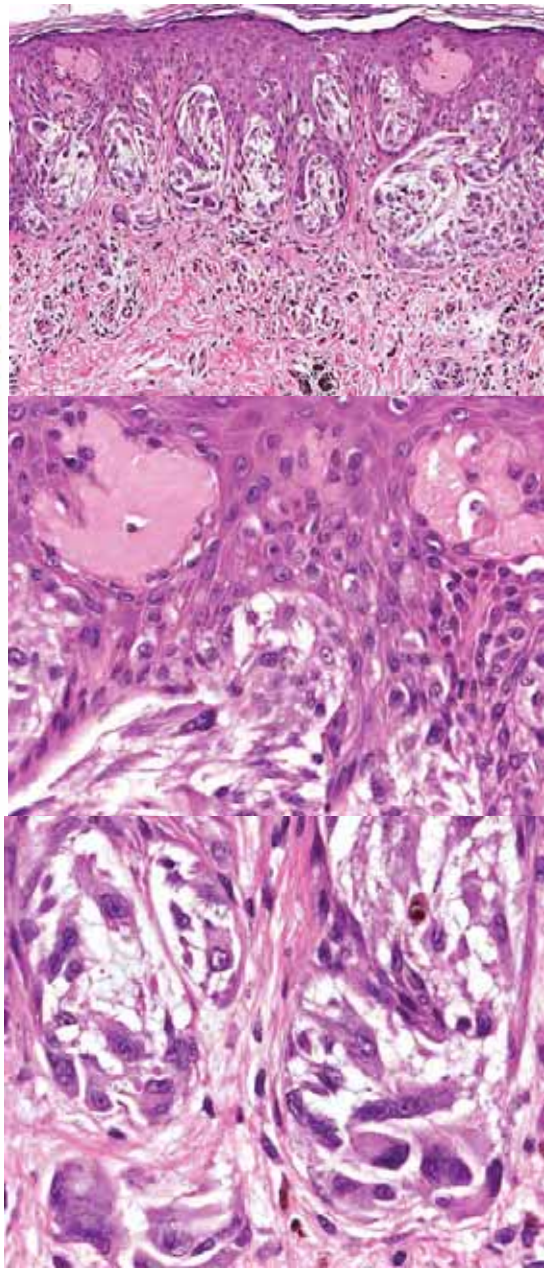
Spitz nevus



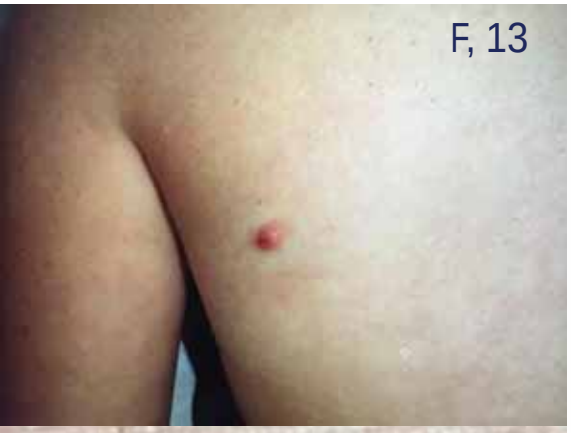


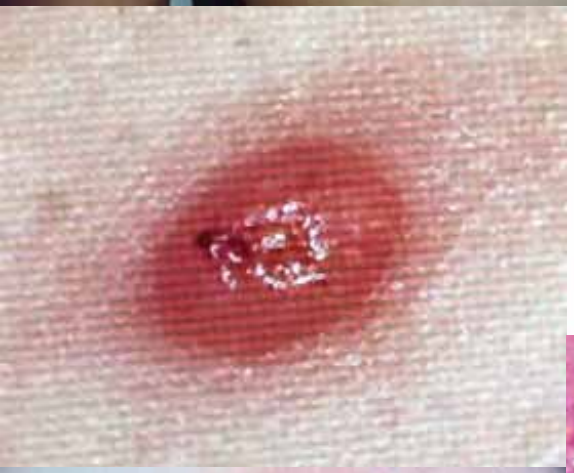


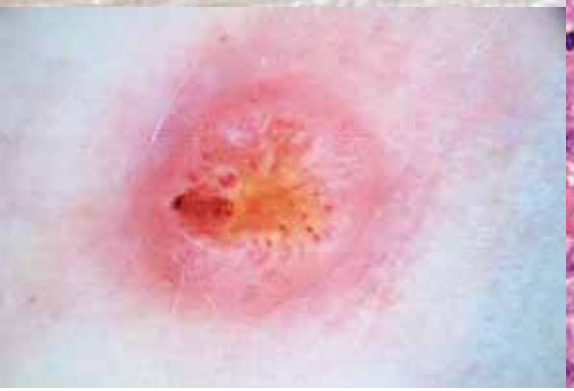


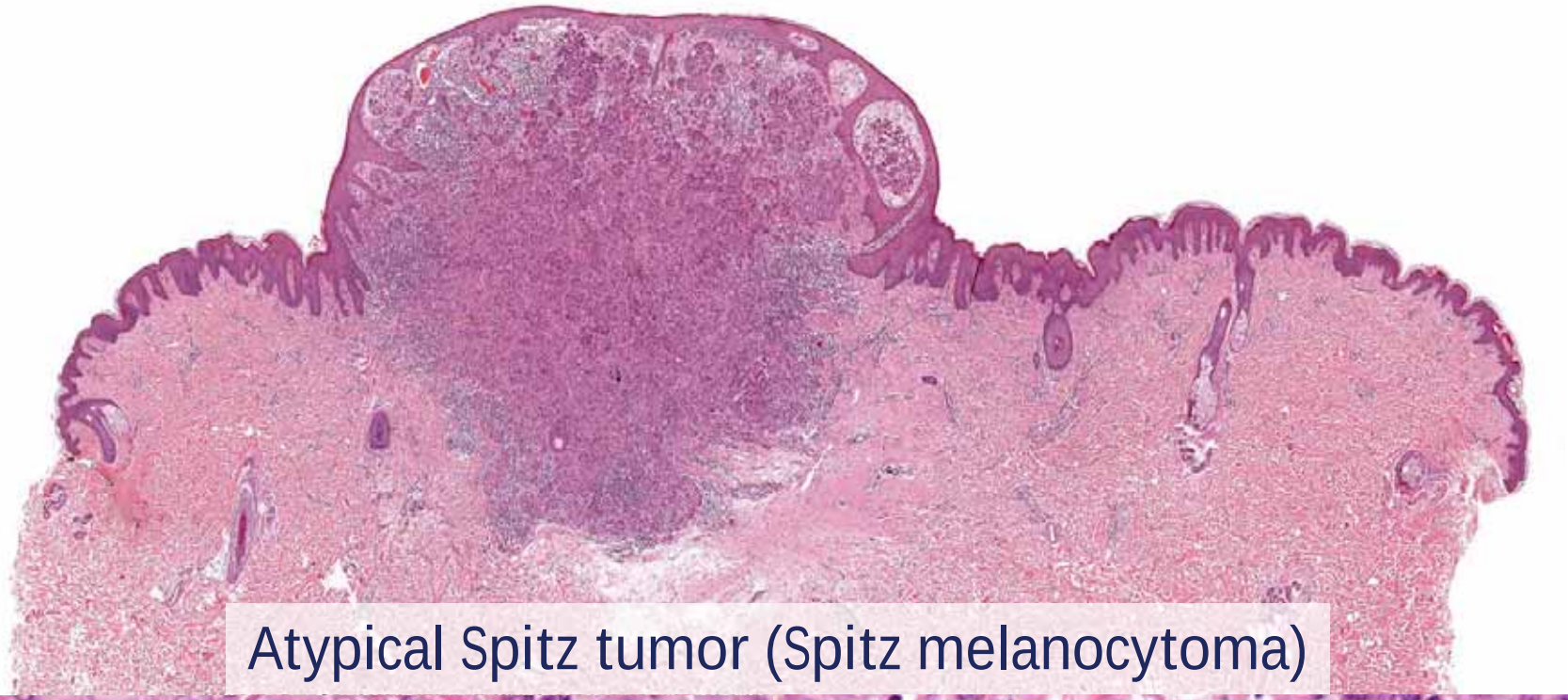


Spitz nevus

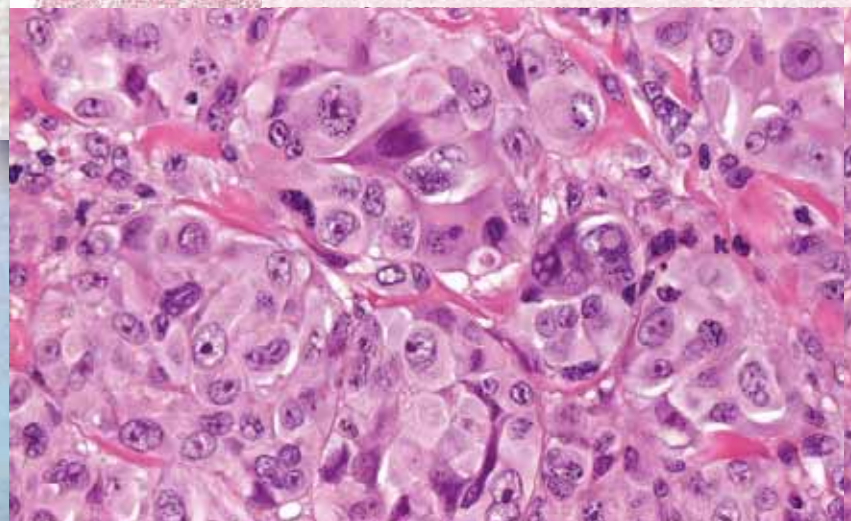


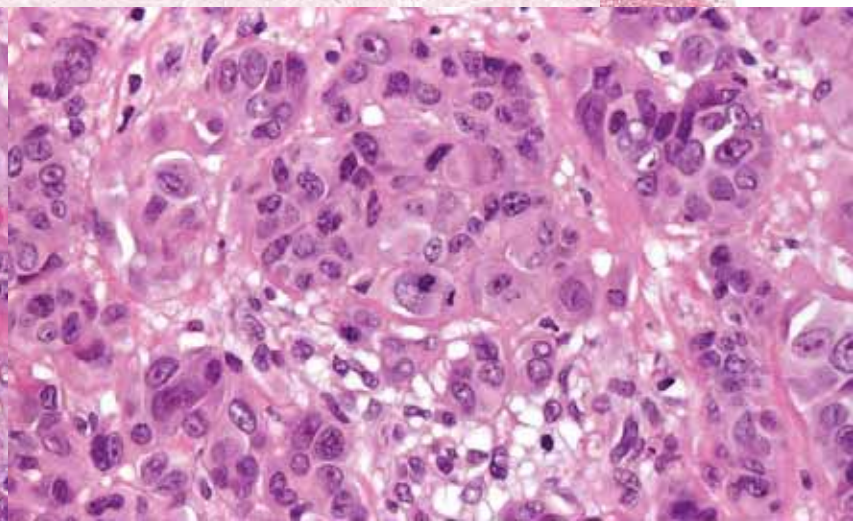


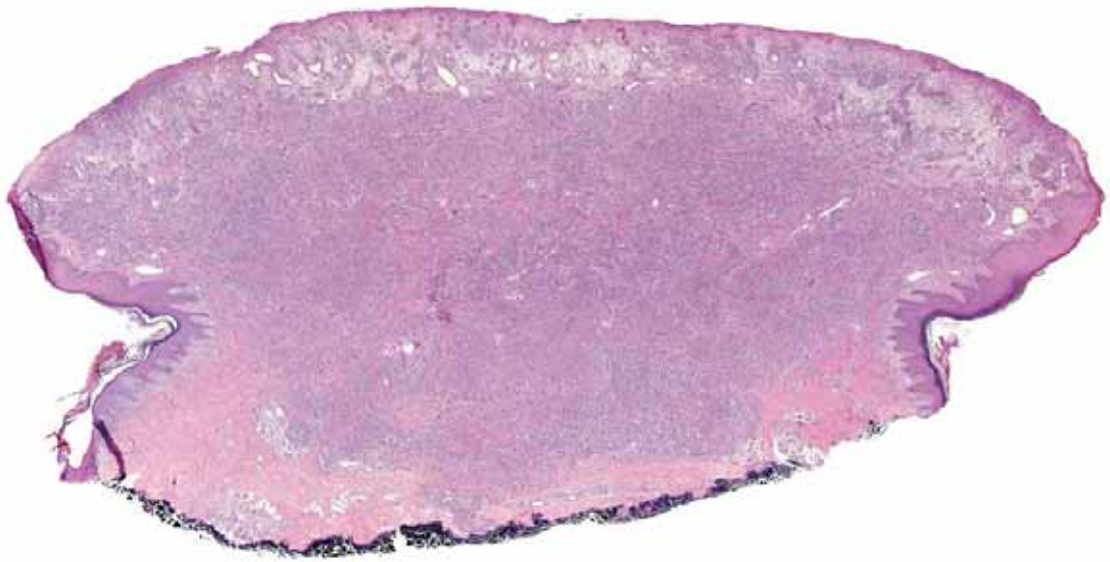


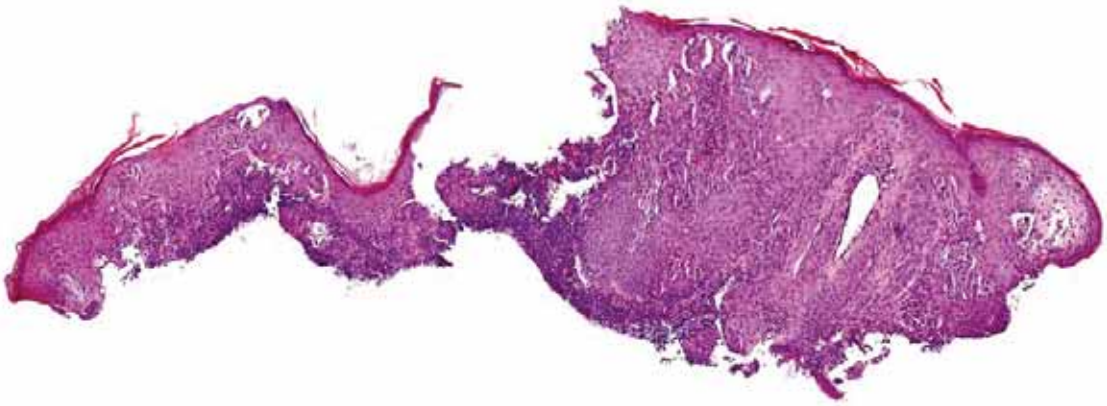


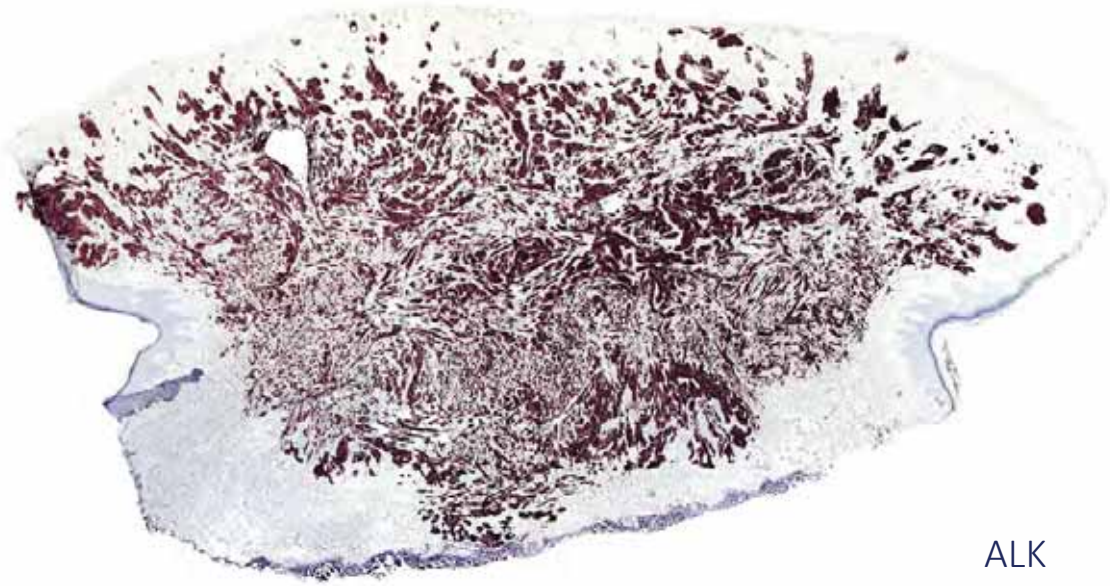
Atypical Spitz tumor (Spitz melanocytoma)



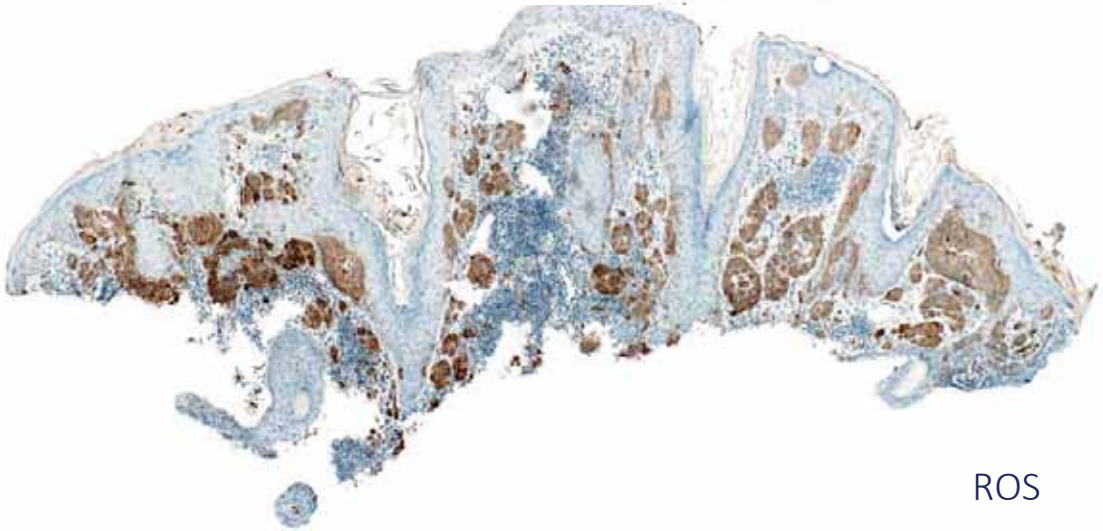








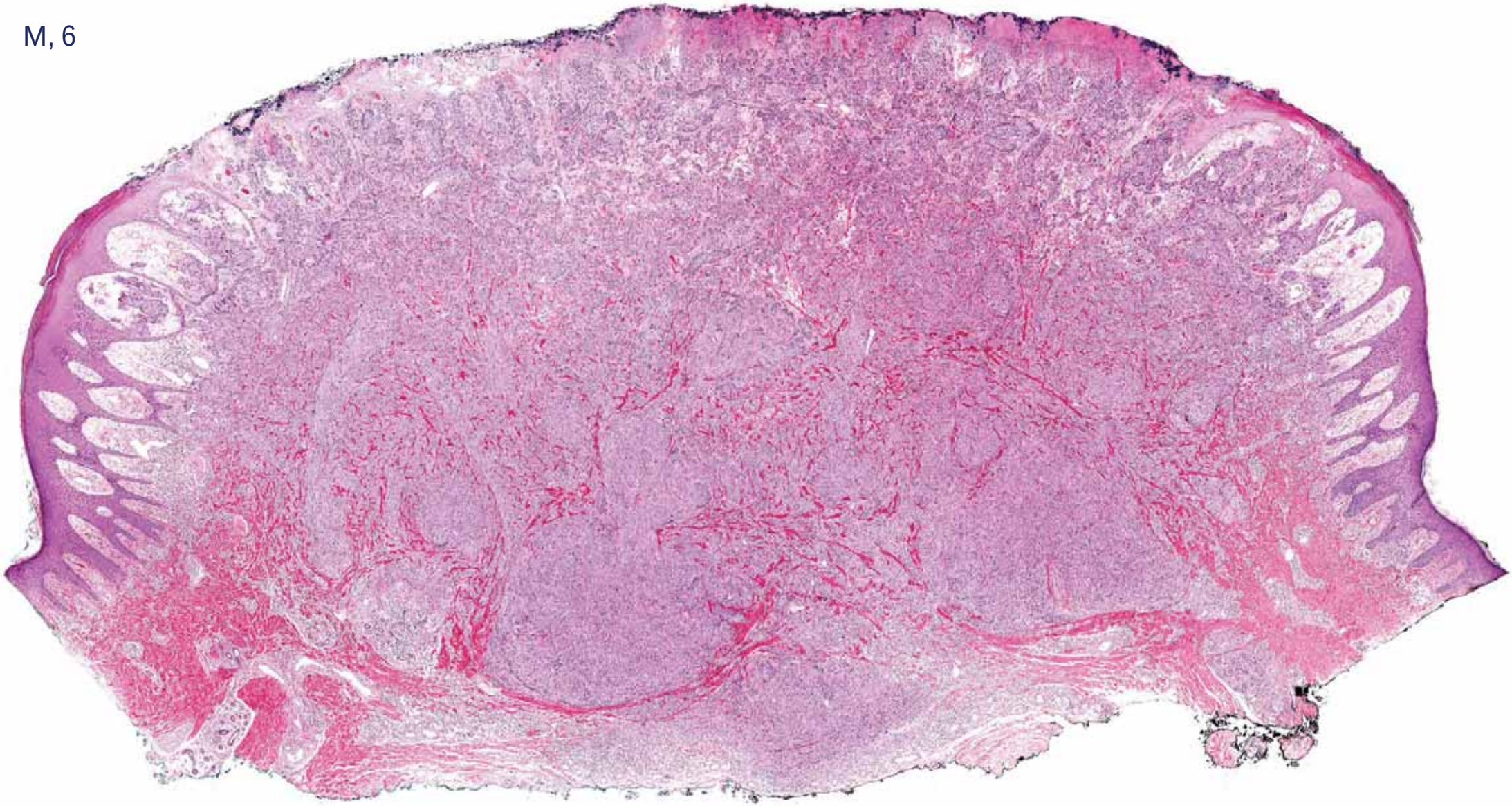
ALK



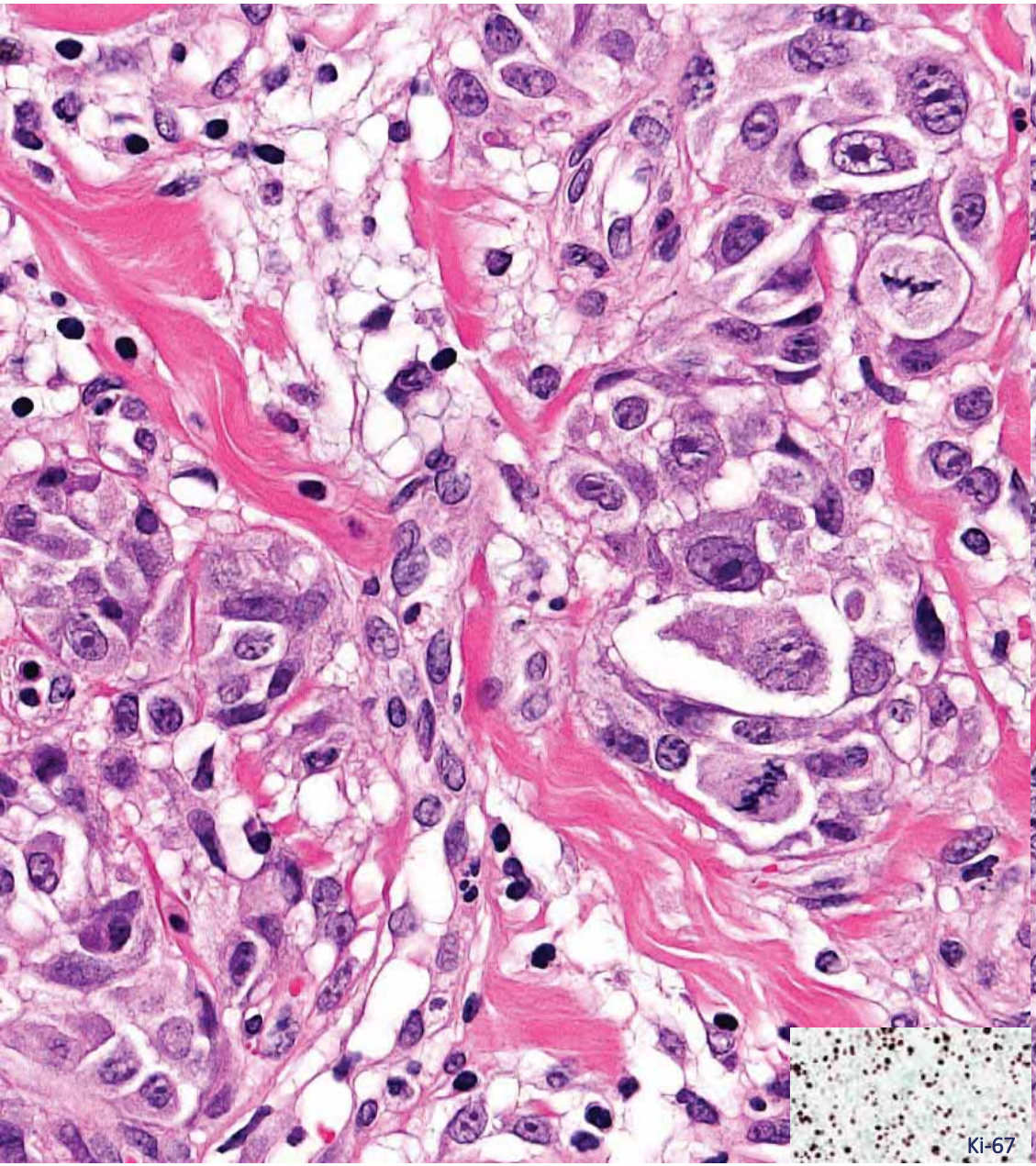
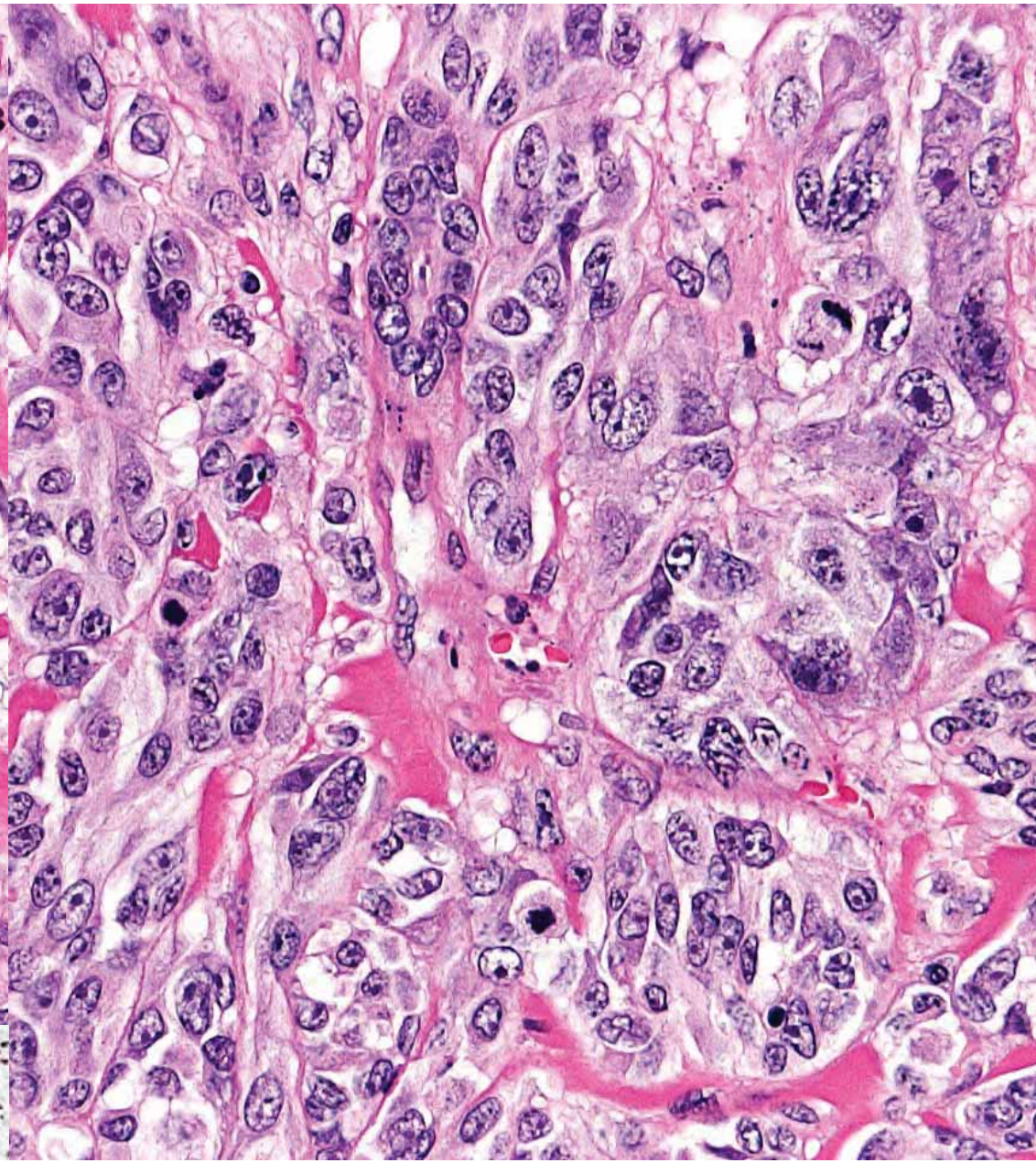
ROS

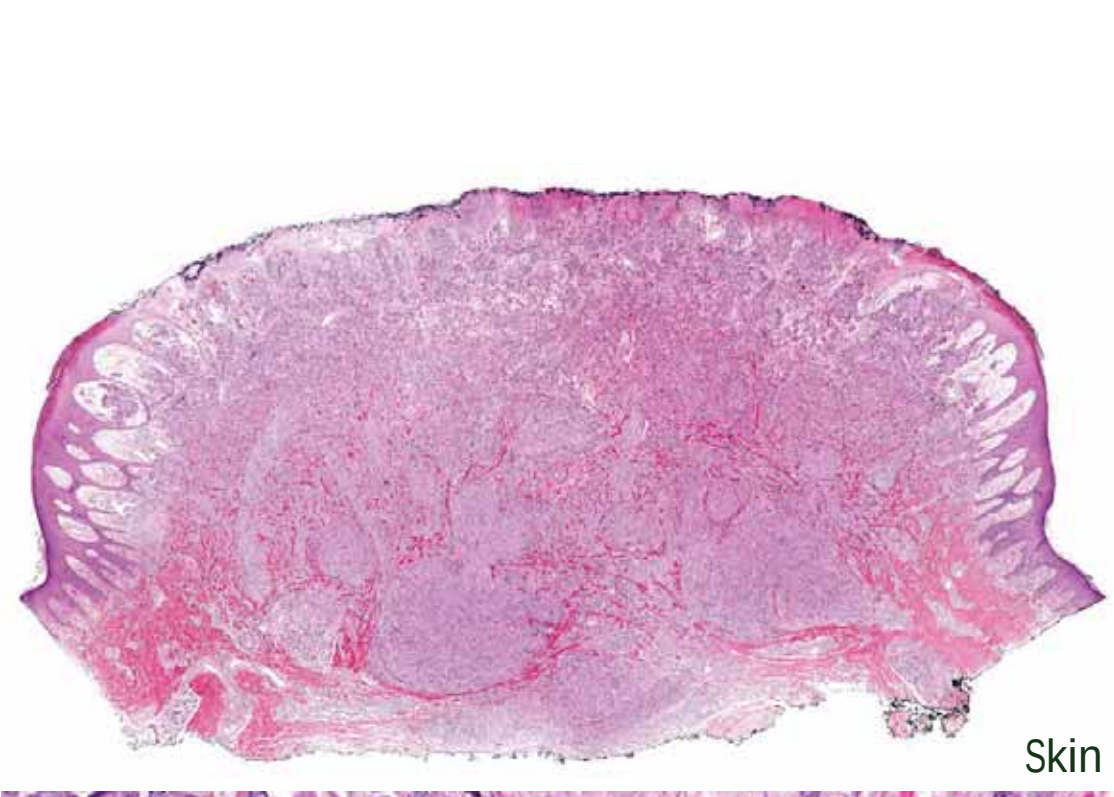
Immunohistochemical stainings are available to identify some of the fusions of atypical Spitz nevi/tumors; they allow to put the tumor in a specific subgroup, but do not have any value in the differentiation of benign from malignant lesions. At present, they are not necessary in the histopathological evaluation of these tumors *(my view).*

M, 6

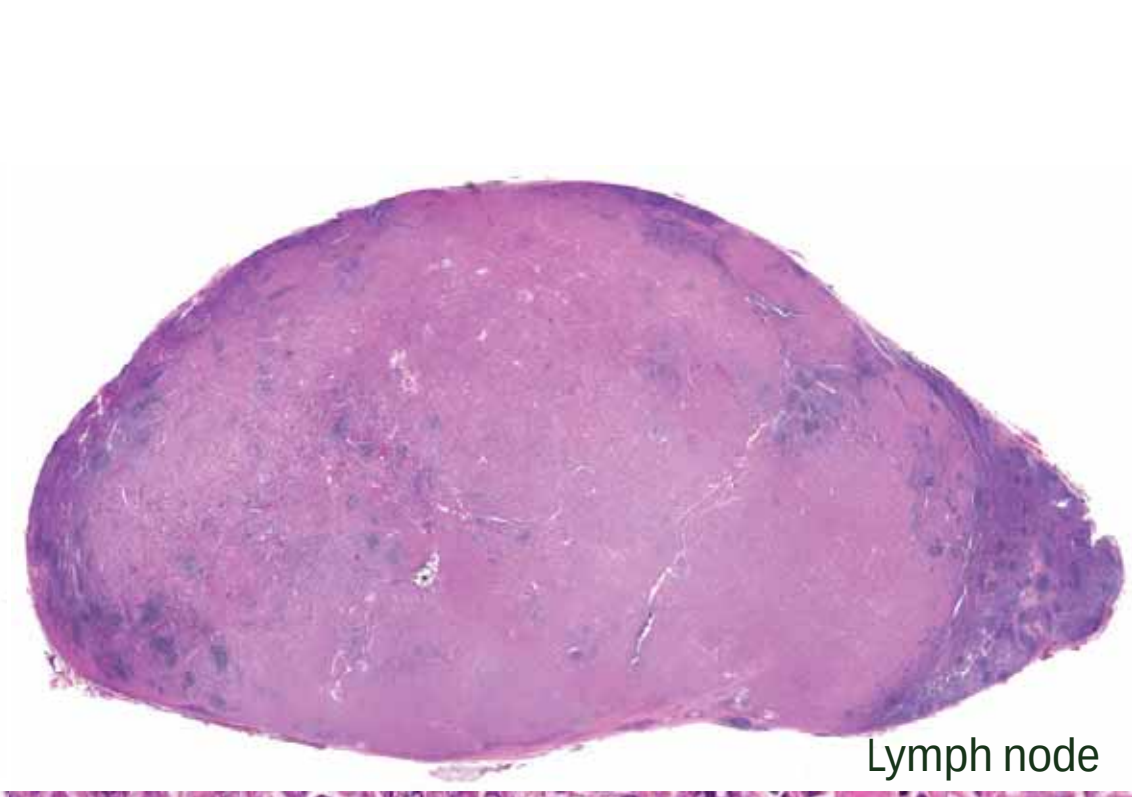


Spitz melanoma

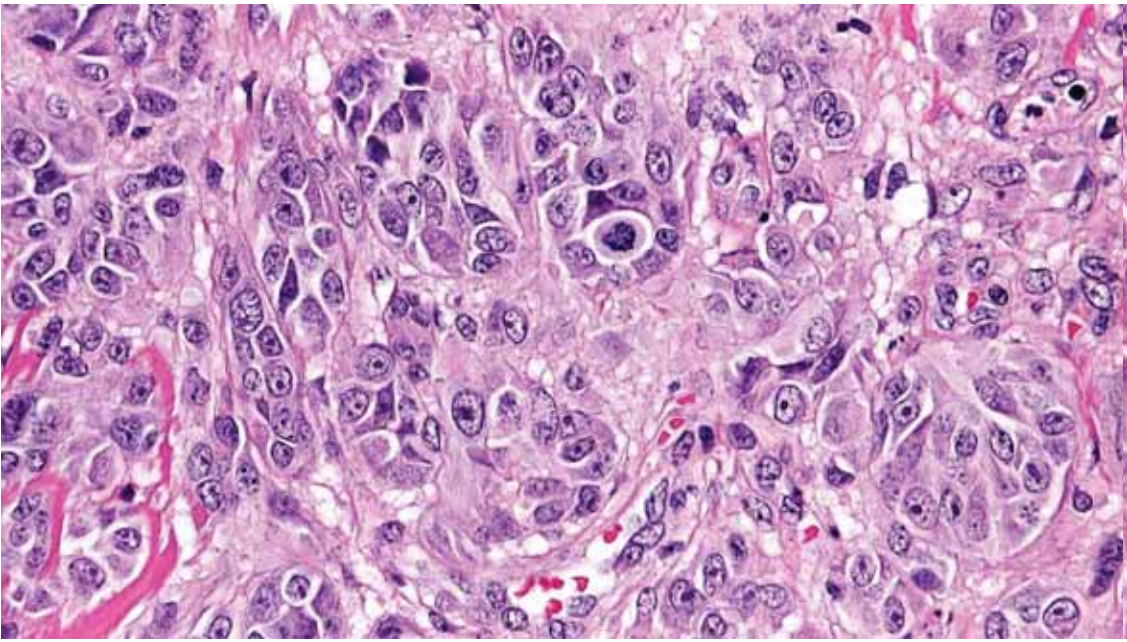

Ki-67


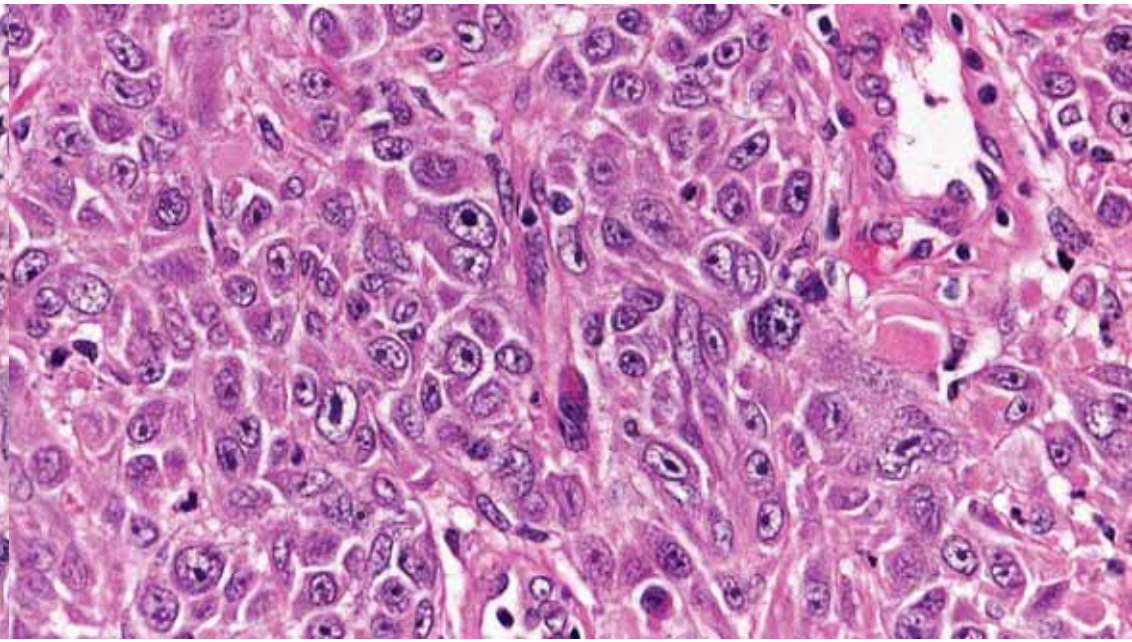


Skin

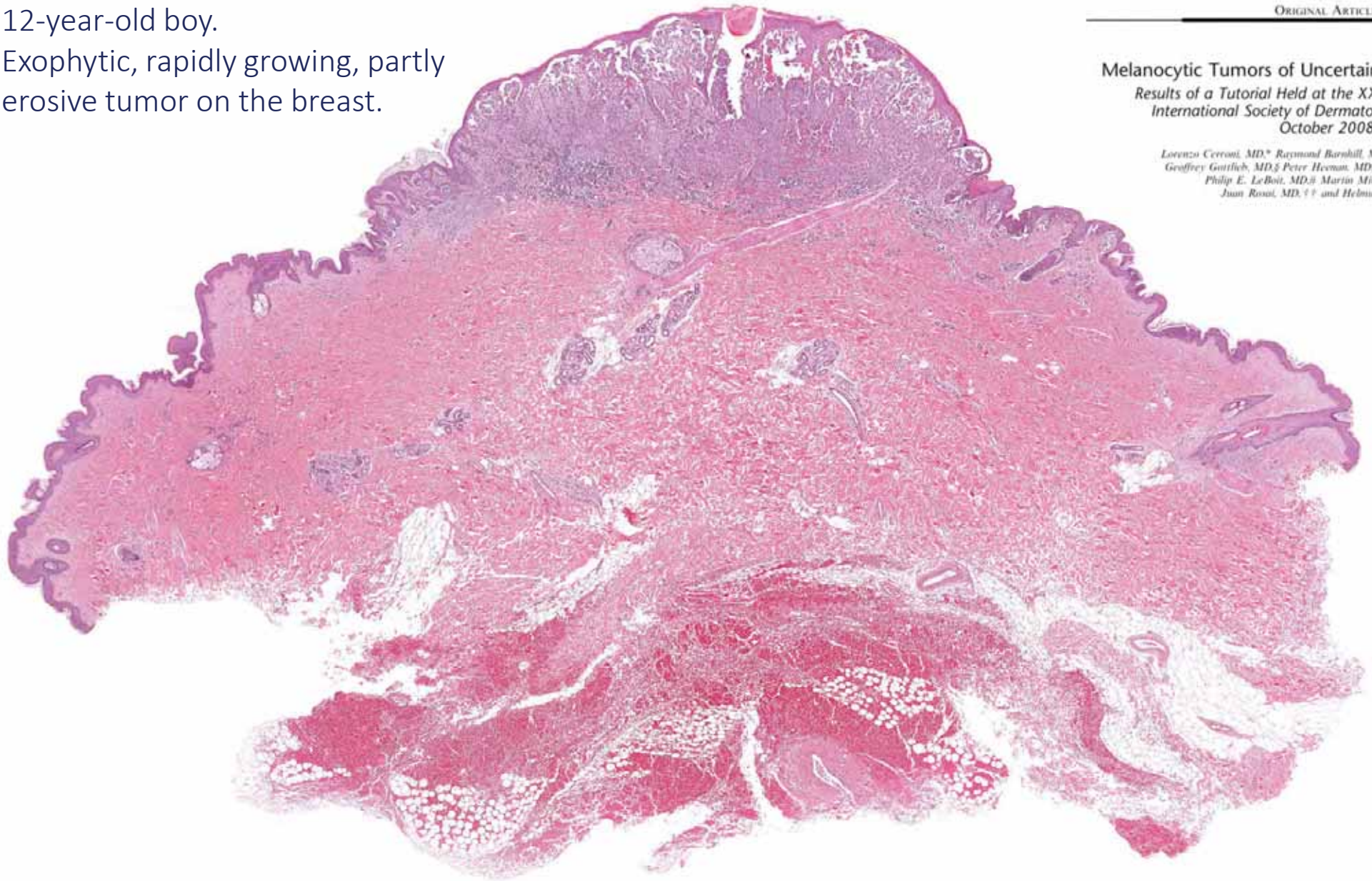


Lymph node





12-year-old boy.
Exophytic, rapidly growing, partly erosive tumor on the breast.

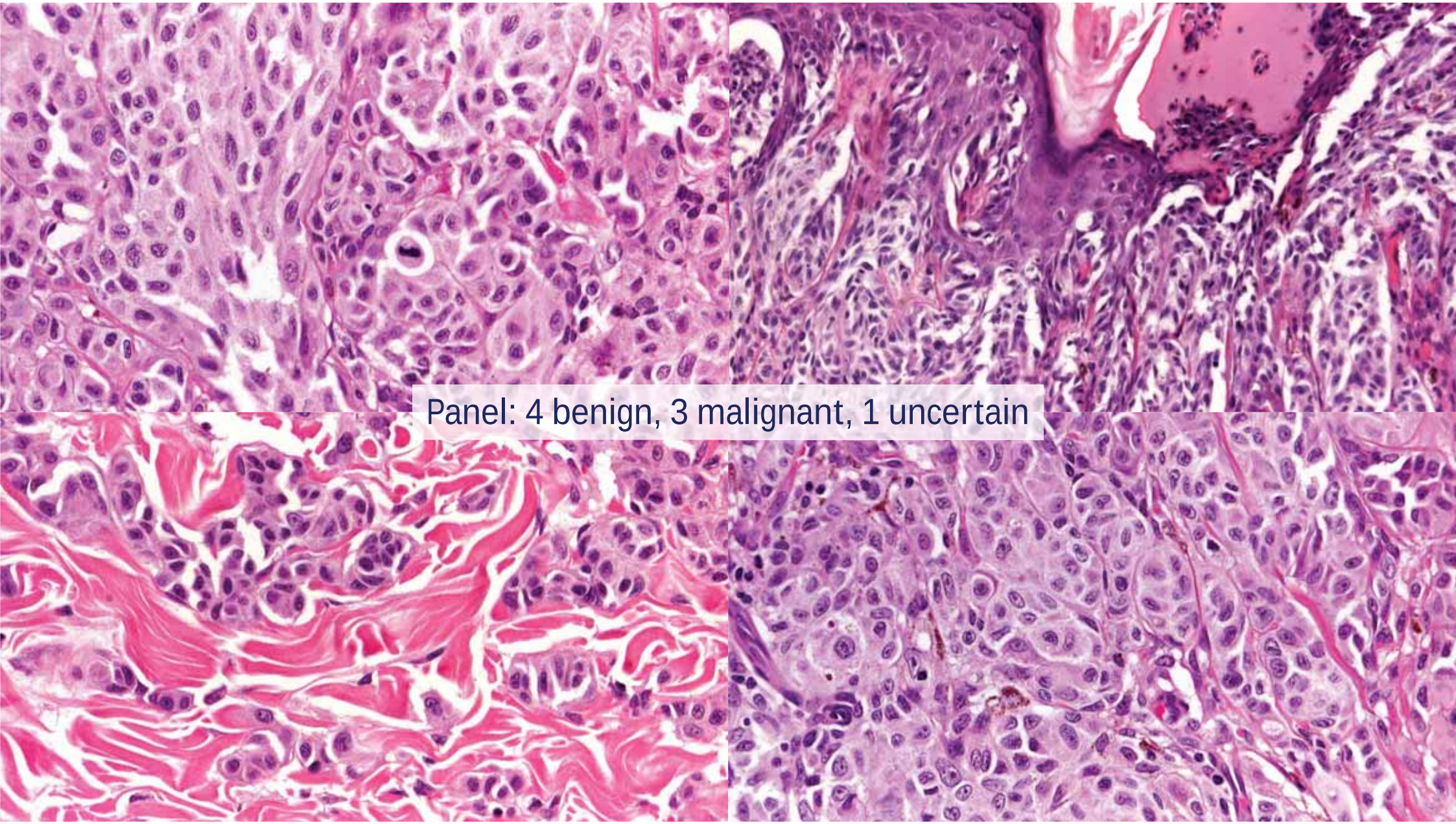


ORIGINAL ARTICLE

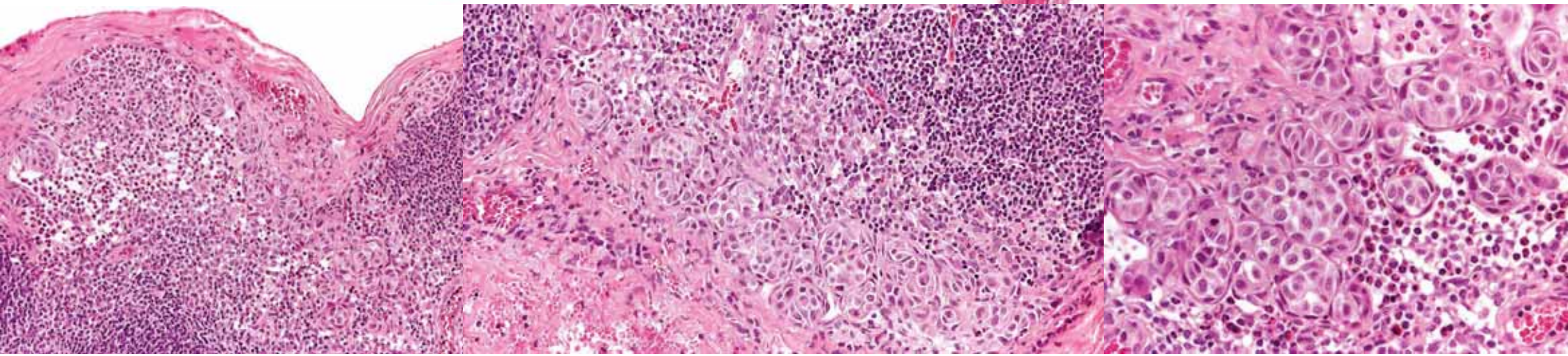
Melanocytic Tumors of Uncertain Malignant Potential

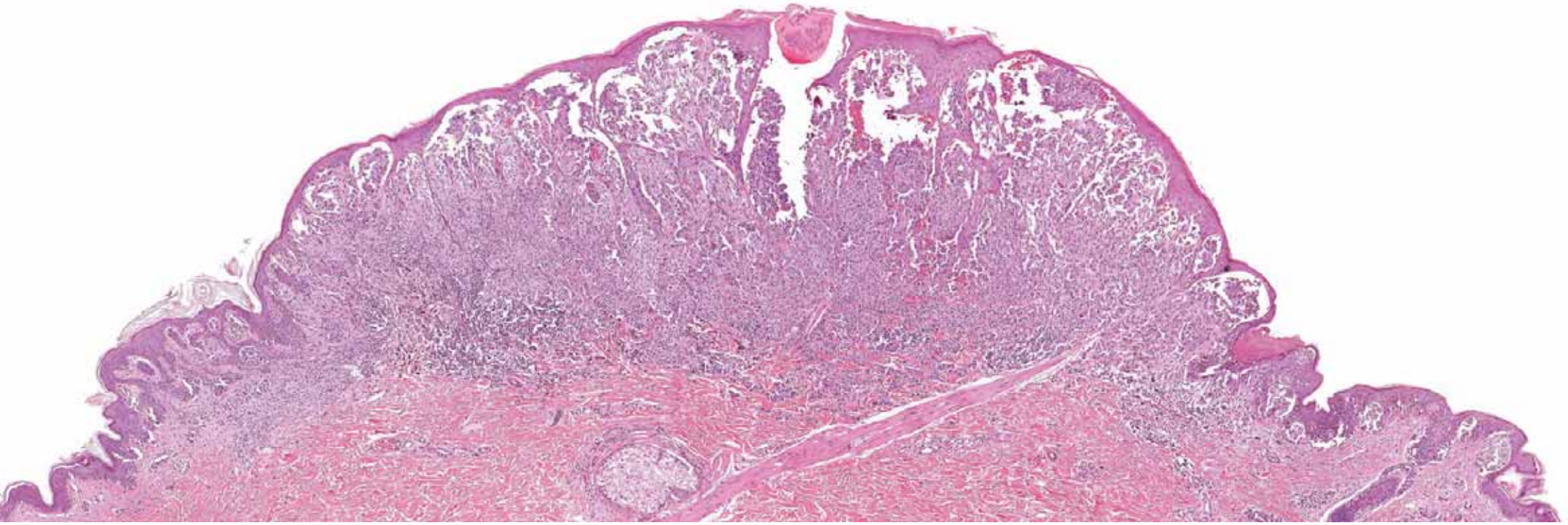
Results of a Tutorial Held at the XXIX Symposium of the International Society of Dermatopathology in Graz, October 2008

Lorenzo Cerroni, MD, Raymond Barnhill, MD,† David Elder, MD,‡ Geoffrey Gottlieb, MD,§ Peter Heenan, MD,‖ Heinz Kutzner, MD,¶ Philip E. LeBoit, MD,# Martin Mihm, Jr, MD,** Juan Rosai, MD,†† and Helmut Kerl, MD**


Panel: 4 benign, 3 malignant, 1 uncertain

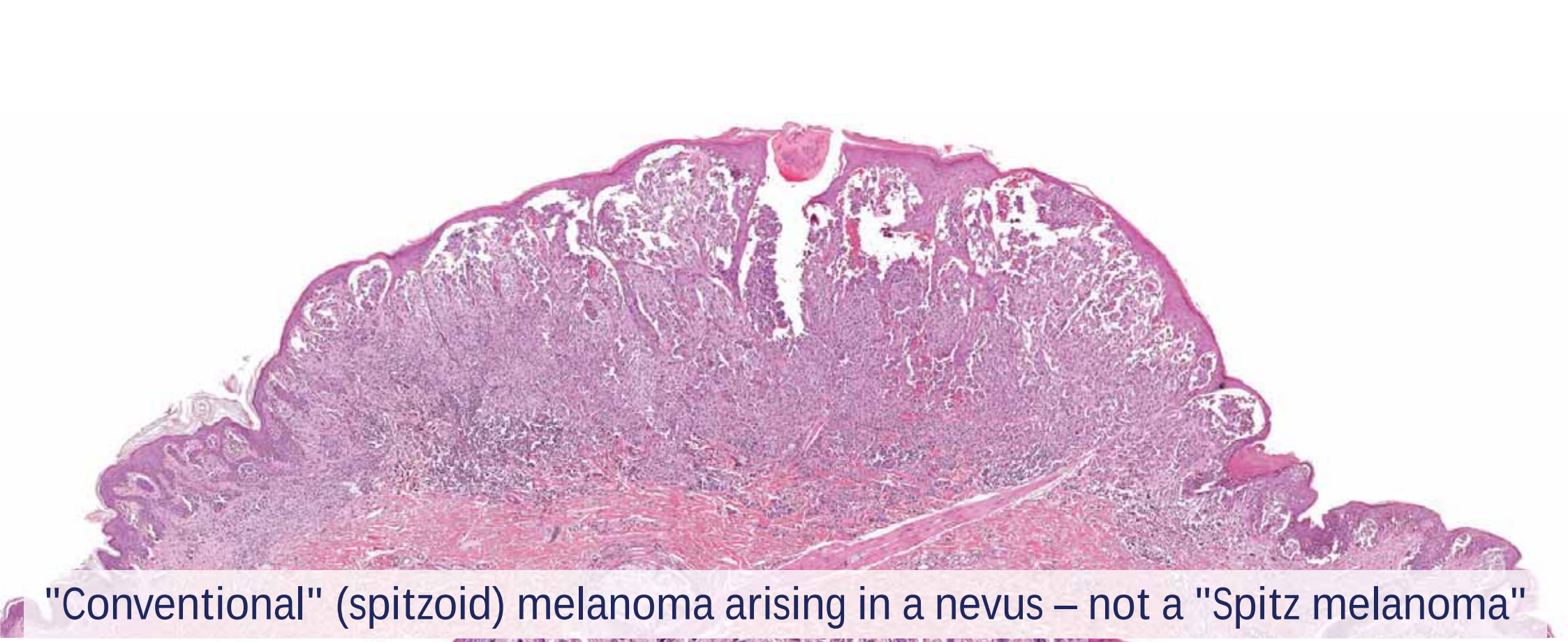
Sentinel lymph node biopsy



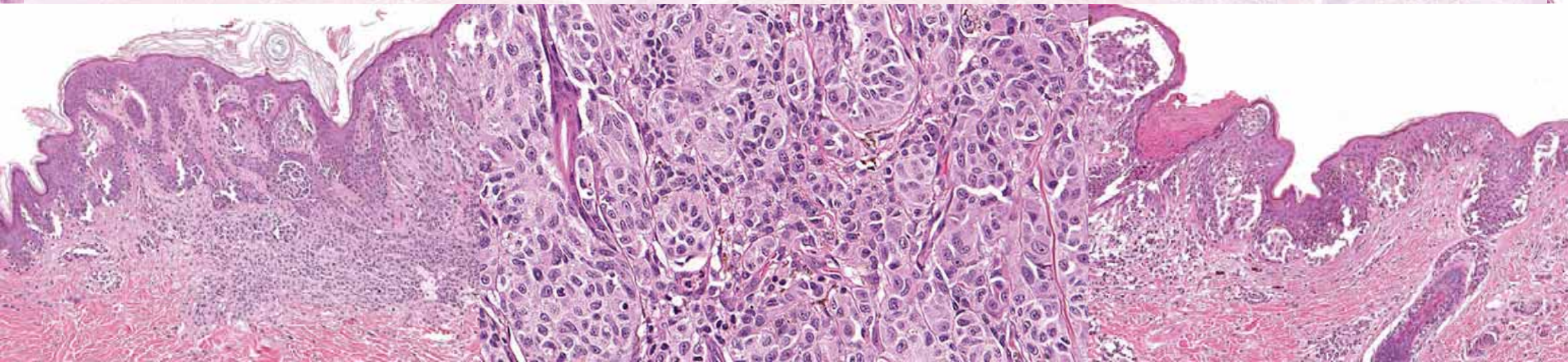


- Primary tumor (12/1999)
- Sentinel LN positive (1/2000)
- Multiple metastases in lungs, kidneys, liver, spleen, orbita, brain (12/2006)
- Death of progressive disease (7/2008)

Spitz melanoma ?



"Conventional" (spitzoid) melanoma arising in a nevus – not a "Spitz melanoma"



Does a "Spitz nevus" exist?

- "Spitzoid" melanocytes *(large epithelioid cells with abundant eosinophilic or amphophilic cytoplasm and large vesicular nuclei that contain prominent nucleoli)* are neither restricted to tumors of the "Spitz lineage", nor to benign melanocytic tumors
- The cases reported by Sophie Spitz were remarkably heterogeneous, and she did not provide precise criteria for identification of a histopathologically reproducible group of lesions
- Molecular studies revealed several different genetic alterations related to benign and malignant tumors traditionally classified within the "Spitz" group
- Some melanocytic tumors with spitzoid morphology (e.g., BAP-1 inactivated nevus) are now classified by the WHO in groups separated from that of tumors of the "Spitz lineage" based exclusively on molecular features (e.g., *BRAF* mutations) – yet "BRAF mutated and morphologically spitzoid tumors (BAMS)" have been described…
- In this context, the WHO scheme is a heterogeneous mixture of location-based (i.e., acral, mucosal, cumulative sun-damage), time of onset-based (i.e., congenital), morphological (i.e., blue, Spitz), and molecular classifications
- Within the so-called "Spitz lineage" of the WHO, differentiation between nevus, atypical tumor and melanoma has a limited reproducibility on histopathological grounds, and is far from being uncontroversial on molecular ones as well

For the time being:

Still thinking, still searching, still reflecting,
still making wrong diagnoses,
and still puzzled by a riddle, wrapped in a mystery, inside an enigma…

…and still dreaming of Sophie Spitz, and of a nevus that doesn't exist.