

# Spitz and Reed nevi: acquired or congenital?

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## Objective

Although conflicting with the concept of nevi being hamartomas, to date, Spitz and Reed nevi have been regarded as acquired melanocytic nevi, whereas many other types have already been accepted as being congenital. Here, the reader will find a survey on clinical, dermatoscopic and histopathologic clues suggesting a congenital origin of authentic Spitz nevi. Relevant differences in respect to Reed nevi are pointed out.

## What is a nevus?

In classic pathology, the term nevus is usually related to a benign hamartomatous proliferation programmed during embryologic life, i.e., a malformation consisting of tissue elements normally found at the corresponding site, but which are growing in a disorganized mass (Latin, *naevus*, birthmark) [1]. Thus, per definition, a nevus has to be of congenital origin, e.g., as a consequence of post-zygotic mutation. However, to date, melanocytic nevi are dichotomized into congenital or acquired ones, although the denomination “acquired nevus” is an oxymoron, the term “congenital nevus” tautological. Fittingly, the concept of nevi being hamartomas was recently weakened by Happle, who suggested defining a nevus rather as a functional or genomic mosaicism, including congenital, but also acquired lesions [2,3].

## Which are the features of congenital nevi?

There are several features suggesting a congenital origin of a melanocytic nevus. By clinical definition, a melanocytic nevus is of the congenital type if present since birth or appearing only shortly after, or if the lesion is of great extension [4]. Additionally, from a pathogenetic point of view, any combined, agminated or systematized growth or the presence of terminal hair follicles should be regarded as indicative of a congenital lesion [1,4]. However, the true time of onset of a given melanocytic nevus may precede its visual perception on the skin surface by months or years and might be accelerated by UV-irradiation or hormonal influences, thus simulating a putatively acquired lesion [5-9].

Pathologists commonly make the diagnosis of a congenital type nevus even in adults based on the presence of particular histopathologic features that may be found in definitely congenital nevi, in particular, infiltration of the reticular dermis or subcutis and involvement of cutaneous appendages, vessels or nerves. As a common finding, melanocytes splay between collagen bundles singly or in double rows [4,10,11]. Recently, the presence of largish melanocytic nests has been identified as a further clue to congenital type nevi and their distinction from acquired ones [4,12,13], although largish nests might also be found in the periphery of growing Clark nevi [14]. Melanocytes of congenital nevi may be of largish

size and comprise fusiform, epithelioid, or even ballooned or neuroid shapes. The overall silhouette of superficial and deep or deep congenital nevi like Zitelli nevus, Miescher nevus or blue type nevi is band-like or, more frequently, wedge-shaped [1].

From a dermatoscopic point of view, congenital type nevi frequently exhibit nuances of a globular pattern [4,9,15].

## Which are the features of acquired nevi?

There is still no universally accepted classification of acquired melanocytic nevi [9]. Traditionally, at least from a clinical point of view, any smaller nevus with an appearance after the first year of life is termed acquired, although, according to Ackerman and other authors, melanocytes that constitute an acquired nevus must already have been present in the skin from the time of parturition and, almost certainly, those melanocytes do not migrate into the skin after birth [1,8,16]. Thus, most acquired nevi might root on congenitally preformed depositions of melanocytes, as may be occasionally seen as an incidental finding in skin sections, thus actually representing tardive congenital nevi [1,17]. However, among clinicians, dermatoscopists and dermatopathologists, Clark nevus, in particular, is unanimously accepted as an authentic acquired melanocytic proliferation and thus arbitrarily chosen as the prototype of an acquired melanocytic nevus [4,9,15].

Interestingly, in contrast to most other types of nevi, Clark nevi are flat, superficial and horizontally oriented proliferations that never involve the reticular dermis or subcutis [1,4,18,19]. In contrast to congenital nevi, the melanocytes of Clark nevi are usually monomorphous and small with an oval shape [1].

From a dermatoscopic point of view, acquired melanocytic nevi like Clark's frequently exhibit a monotonous reticular pattern [4,15,20].

## Features of Spitz nevi

Spitz nevi are rapidly growing red or brown papules or nodules usually developing in children or young adults [1,21]. Up to 7% of Spitz nevi have been reported to occur congenitally and may vary in size from a few millimeters to 2 cm or more [7,21-23]. They may occur in a systematized or agminated pattern and may occasionally be found as constituents of different variants of combined congenital nevi like speckled lentiginous nevi or in association with blue type nevi [21,22,24-38].

Histopathologically, Spitz nevi are dome-shaped superficial or wedge-shaped superficial and deep melanocytic pro-

liferations with a nested, vertical growth pattern composed of largish, polymorphous, fusiform or epithelioid, in part multinuclear melanocytes ("Spitz cells") [1,21,39]. Balloon cells may rarely be seen [40]. Spitz nevi exhibit a prominent epidermal or infundibular hyperplasia possibly associated with syringoadnexotropism, neurotropism or myotropism [21]. In the center, melanocytes disposed as solitary units or in nests may be present above the dermoepidermal junction, here exhibiting a certain transepidermal maturation inversely to such usually seen in dermal melanocytic populations [41]. Fibroplasia may be impressive, in particular in dermal variants of Spitz nevi [22].

Dermatoscopically, Spitz nevi are typified by nuances of a globular pattern, frequently associated with a structureless center [4,42].

## Features of Reed nevi

Reed nevi are rapidly growing brown or black, flat or slightly raised lesions usually developing in young adults. Only few Reed nevi have been noted at birth [43]. Histopathologically, Reed nevi are typified by a superficial horizontal fascicular growth pattern restricted to the epidermis and papillary dermis and a strong melanin pigmentation [44]. They consist of monomorphous fusiform or sometimes epithelioid melanocytes aggregated in rather largish nests [21,22,39,45,46]. An infiltration of the superficial portions of the eccrine ducts is commonly seen [21,39].

Dermatoscopically, Reed nevi start with a globular pattern. In a more developed stage they are typified by nuances of a unique starburst pattern consisting of circumferential radial lines or pseudopods and a structureless center. Later, the starburst pattern may disperse into a rather reticular pattern [4].

## Discussion

Most types of melanocytic nevi like Unna's, Miescher's, Clark's or Spitz's were originally considered to be acquired melanocytic nevi [18,19]. Meanwhile, several parallels between unambiguously congenital and apparently acquired nevi were recognized and, recently, at least blue type nevi, Miescher nevus and Unna nevus have been accepted as congenital type melanocytic nevi [1,4,9,21,47]. In contrast, although conflicting with the concept of nevi being hamartomas, to this day, Spitz and Reed nevi are still regarded as acquired melanocytic nevi [18,19,21].

However, in several descriptions of Spitz nevus it has been noted to have features in common with superficial or superficial and deep congenital melanocytic nevi, too [21,22]. In 2000, Harris et al compared congenital and acquired Spitz

nevi with superficial congenital nevi from a clinical and histopathologic point of view, also recognizing many overlapping features [23]. Although Ackerman in 2007 distinguished congenital and acquired Spitz nevi [21], Harris et al seem to be the first and only so far seriously considering a congenital origin of any authentic, that is, not atypical, Spitz nevus [23].

In point of fact, the burden of clues indicating a congenital origin of Spitz nevi seems striking: Spitz nevi have a preponderance for children or young adults, and up to 7% of the lesions have even been reported to occur congenitally [7,21-23]. They may vary in size from a few millimeters to 2 cm or more, an extension usually regarded as incompatible with the diagnosis of an acquired nevus [4,7]. Spitz nevi may occur in a systematized or agminated pattern, including satellite lesions, strongly arguing for a predetermination early in embryologic life [21,22,24-32]. Additionally, they may occasionally be found as constituents of different variants of combined congenital nevi like speckled lentiginous nevus or in association with blue type nevi [33-38]. According to Ackerman, all constituents of a combined nevus should represent congenital type nevi [1,21]. Thus, even from a clinical point of view, Spitz nevi actually should be regarded as truly congenital melanocytic nevi, although their clinical manifestation may be obvious many years later, only if dormant nevi become abruptly activated upon hormonal stimulation during puberty or pregnancy [7].

Interestingly, to date, there do not seem to be any consistent reports on combined nevi consisting of any truly acquired constituent like Clark nevus. The unique report by Marghoob et al on the case of agminated atypical seems to be based on a misinterpretation, as the provided figures exhibit the clinical, dermatoscopic and histopathologic features of an agminated superficial congenital nevus (Ackerman nevus), incompatible with the considered diagnosis of agminated Clark nevus [48]. In addition, Ackerman described Clark nevi as constituents of combined nevi in association with blue or Spitz nevi [1]. Here, in our opinion, the putative Clark nevus most likely corresponds to an associated Unna or Ackerman nevus, respectively, as the melanocytes are either confined to the expanded papillary dermis or the junctional melanocytic nests are too large for an authentic Clark nevus [1,12]. Finally, the dysplastic compound nevi associated with agminated Spitz nevi reported by Hamm et al most likely represent associated (incipient) superficial congenital melanocytic nevi [26].

Histopathologically, Spitz nevi are superficial or superficial and deep melanocytic proliferations composed of largish, fusiform or epithelioid, in part multinuclear melanocytes ("Spitz cells") aggregated in largish, predominantly vertically oriented nests [1,21]. Fittingly, melanocytes of congenital nevi are also largish and tend to a rather spindled shape than those of truly acquired Clark nevi. Additionally,

multinucleate melanocytes are an expected finding in congenital type nevi like Unna or Miescher nevi, but virtually never seen in acquired nevi like Clark's [1]. Thus, the occurrence of large and multinucleate melanocytes in about 25% of the lesions analyzed by Requena et al might be another clue to the congenital nature of Spitz nevi [49]. Interestingly, those "Spitz cells" also might occasionally be met with in combined congenital melanocytic nevi, Miescher nevi, balloon cell nevi or deep penetrating nevi [21]. Balloon cells, however, as occasionally found in other congenital nevi, may only rarely be seen [40].

The prominent epidermal or infundibular hyperplasia together with a possible adnexotropism (in particular, syringotropism), neurotropism or myotropism suggests Spitz nevi to represent hamartomatous proliferations [21]. In the center, melanocytes disposed as solitary units or in nests may be present above the dermoepidermal junction, as may be seen in early congenital melanocytic nevi, here exhibiting a certain transepidermal maturation inversely to that usually seen in dermal melanocytic populations [1,41].

Interestingly, Spitz nevi may infiltrate the deeper reticular dermis and even the subcutaneous fat, paralleling the vertical and wedge-shaped growth pattern of Miescher nevus [21]. Rarely, however, Spitz nevus may also present as a sessile or papillomatous papule, thus exhibiting a pattern reminiscent of that seen in Unna nevus [21]. Fibroplasia may be impressive in dermal variants of Spitz nevi being reminiscent of that seen in blue type nevi [22].

Dermatoscopically, as many other congenital type nevi, Spitz nevi are typified by nuances of a globular pattern [4,42]. However, the initial rapid growth of Spitz nevi, some overlapping features with melanoma as well as the lacking reports on terminal hair growing within Spitz nevi, a finding generally indicating the congenital nature of a given melanocytic nevus [21], might be considered as clues to a rather acquired histogenesis. Furthermore, some findings like fibroplasia, epidermal or infundibular hyperplasia, and infiltration of eccrine ducts or largish melanocytes may be a feature of both melanoma and Spitz nevus, thus again relativizing their implication as clues to a congenital nature.

According to Ackerman, Spitz nevus exhibits the silhouette of an acquired melanocytic nevus. Ackerman, however, did not define precisely the criteria of the silhouette of an acquired nevus in contrast to such of a congenital one [21]. Nonetheless, Ackerman regarded agminated or systematized Spitz nevi and those being present since birth as truly congenital, i.e., hamartomatous, the others as their acquired analogues [21].

This does not seem plausible to us, as a veritable Spitz nevus is either congenital or acquired. Otherwise acquired or congenital types must be differing entities with morphologic overlap only. Obviously, the silhouette of some Spitz nevi

may be reminiscent of that of Miescher nevus, blue nevus or even Unna nevus, all the three representing nevi that have already been accepted as being of the congenital type.

In contrast, Reed nevi strongly imitate the silhouette of Clark nevus, so far the only melanocytic nevus with even molecular clues to a truly acquired origin [50].

It has been assumed that a point mutation V600E in the B-RAF gene corresponds to a somatic defect that can be induced by intermittent sun exposure and may be an early step in the genesis of melanoma and (acquired) melanocytic nevi [51]. Interestingly, Spitz nevi, blue nevi and classic congenital melanocytic nevi obviously do not possess that mutation, but harbor mutations in the C-KIT, C-MET or N-RAS genes instead [9,52-54]. Hence, the lack of B-RAF mutations might be another indirect argument pointing towards a congenital nature of Spitz nevi. Unfortunately, for the time being there is no molecular data available explicitly referring to Reed nevus.

In contrast to Spitz nevus, the indicators of a congenital origin of Reed nevus are poor. The outstanding reports on agminated or systematized Reed nevi, or Reed nevus as constituent of a combined nevus, rather suggest a histogenetic event compatible with what is regarded to be a truly acquired melanocytic nevus and might represent another clue to Reed and Spitz nevi being different entities. Finally, a review of the corresponding figures published in relevant reports did not result in identification of any agminated or combined nevus seriously suspicious for Reed nevus.

Histopathologically, Reed nevi are typified by a horizontal fascicular growth pattern restricted to the epidermis and papillary dermis [21,39,44], thus paralleling the pattern of Clark nevus. However, the prevailing cytomorphologic feature of spindle-shaped or even epithelioid melanocytes seem to be more in favor of a congenital type nevus. However, as mentioned for Spitz nevi, no terminal hair follicles have been reported to occur in Reed nevi yet. Reed nevi and Spitz nevi have in common an infundibular accentuated epidermal hyperplasia and a frequent melanocytic infiltration of the upper eccrine ducts [21].

Dermatoscopically, Reed nevi start with a globular pattern indistinguishable from that of Spitz or other congenital type nevi. In a more developed stage they are typified by nuances of a unique starburst pattern consisting of circumferential radial lines or pseudopods. Later, the starburst pattern may disperse into a reticular pattern reminiscent of that seen in Clark nevus [4].

In 2007, Argenziano et al proposed a classification system for melanocytic nevi based on dermatoscopic features [15]. They distinguished congenital nevi present at birth or appearing before puberty with a globular pattern, whereas acquired nevi usually exhibit a reticular pattern. According to the dual concept of neogenesis based on dermatoscopic observations, Zalaudek and coworkers distinguished

an endogenous, i.e., genetically determined pathway represented by a dermatoscopically globular pattern and a rather vertical growth and an exogenous or UV-dependent pathway with associated BRAF mutation dermatoscopically represented by a reticular pattern and a rather horizontal growth [9]. Hence, all melanocytic nevi growing at non-UV-exposed localizations must be of the congenital type, including Spitz nevus which has been reported to grow even at the palate [55]. On the other hand, the possible congenital onset of Reed nevi argues against their UV-dependent acquired histogenesis.

Interestingly, largish junctional melanocytic nests are an expected finding not only in congenital type nevi but in growing lesions, particularly at the periphery of enlarging Clark nevi [14]. As a consequence, the presence of a globular dermatoscopic pattern of Reed and Spitz nevi might only be an expression of their rapid growth and not a reliable proof of their acquired or congenital nature. A truly acquired origin of Reed nevi would, however, implicate at least one more pathway within the dual concept of neogenesis advocated by Zalaudek et al [9], an additional UV-independent exogenous pathway. An alternative concept was recently suggested by Happle, who proposed a functional or genomic mosaicism that might be congenital, but also acquired anytime during life, as origin of any nevoid growth. Hence, the definition of nevus must not inevitably include the idea of a hamartomatous proliferation and, furthermore, an authentic nevus might be actually acquired, among other possible factors, such as following chronic or intermittent UV exposure [2,3].

To sum up, taking into consideration all the aforementioned clinical, dermatoscopic and dermatopathologic features of Spitz and Reed nevi (Table 1), we propose a congenital origin for all authentic Spitz nevi might be proposed. In contrast, Reed nevi seem to exhibit several features favoring an acquired histogenesis. Owing to the morphologic overlap with Spitz nevus, however, it may be speculated that Reed nevus corresponds to a morphologically distinctive, acquired analogue of Spitz nevus. It might be presumed that both could share a similar genetic disorder acquired at different times during embryologic or postnatal life, which would explain the different clinical settings. However, this might not be a sufficient explanation for their horizontal or vertical growth patterns that, again, might depend on additional local factors.

In conclusion, further comparative and molecular studies on congenital versus apparently acquired Spitz and Reed nevi are required to verify their true histogenetic origin.

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**TABLE 1.** Clues to an acquired or congenital nature of Spitz and Reed nevi.

Reed nevus		Spitz nevus	
Arguments pro congenital origin	Arguments pro acquired origin	Arguments pro congenital origin	Arguments pro acquired origin
<p><b>Clinical</b></p> <ul style="list-style-type: none"> <li>• Congenital onset possible, albeit rarely</li> <li>• Predilection for children or young adults</li> </ul>	<p><b>Clinical</b></p> <ul style="list-style-type: none"> <li>• Rapid growth</li> <li>• No reports on agminated growth</li> <li>• No reports on being constituent of a combined nevus</li> <li>• No reports on occurrence at non-UV-exposed anatomical sites</li> </ul>	<p><b>Clinical</b></p> <ul style="list-style-type: none"> <li>• Congenital onset possible</li> <li>• Predilection for children or young adults</li> <li>• Agminated pattern possible</li> <li>• Occasional constituent of combined nevi</li> <li>• Large size up to more than 2 cm possible</li> <li>• Occurrence at non-UV-exposed anatomical sites</li> </ul>	<p><b>Clinical</b></p> <ul style="list-style-type: none"> <li>• Rapid growth</li> <li>• No reports on associated terminal hair growth</li> </ul>
<p><b>Dermatoscopy</b></p> <ul style="list-style-type: none"> <li>• Initial globular pattern</li> </ul>	<p><b>Dermatoscopy</b></p> <ul style="list-style-type: none"> <li>• Starburst pattern later tapering off into a reticular pattern like Clark nevus</li> </ul>	<p><b>Dermatoscopy</b></p> <ul style="list-style-type: none"> <li>• Globular pattern as seen in other congenital nevi</li> </ul>	
<p><b>Dermatopathology</b></p> <ul style="list-style-type: none"> <li>• Largish nests</li> <li>• Fusiform melanocytes</li> <li>• Epithelioid or multinuclear melanocytes possible</li> <li>• Infundibular hyperplasia</li> <li>• Infiltration of eccrine ducts</li> <li>• Central pagetoid spread of melanocytes possible</li> </ul>	<p><b>Dermatopathology</b></p> <ul style="list-style-type: none"> <li>• Silhouette reminiscent of Clark nevus</li> <li>• Horizontal growth pattern restricted to epidermis and papillary dermis, i.e., no consistent reports on dermal variants involving the reticular dermis</li> <li>• Relatively small melanocytes</li> <li>• No reports on associated terminal hair growth</li> <li>• Some features in common with melanoma</li> </ul>	<p><b>Dermatopathology</b></p> <ul style="list-style-type: none"> <li>• Silhouette may be reminiscent of Miescher or Unna nevus</li> <li>• Infiltrative vertical growth pattern with possible infiltration of the reticular dermis or subcutis</li> <li>• Reports on dermal variants</li> <li>• Largish nests</li> <li>• Epithelioid / multinuclear melanocytes frequent</li> <li>• Infundibular hyperplasia</li> <li>• Infiltration of eccrine ducts</li> <li>• Myotropism, neurotropism</li> <li>• Fibroplasia</li> <li>• Central pagetoid spread of melanocytes possible</li> <li>• No reports on B-RAF mutation</li> </ul>	<p><b>Dermatopathology</b></p> <ul style="list-style-type: none"> <li>• Some features in common with melanoma</li> </ul>

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