

Nevus Spilus: A Review of the Literature

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Abstract

Nevus spilus (NS) is usually the term given to a pigmented skin lesion, either congenital or acquired, consisting of a large light tan patch, containing macules or papules. Usually, these superimposed lesions are numerous, small circumscribed, dark brown in color, flat or slightly raised.

Nevus spilus can be seen anywhere on the body surface, but the most common location is on the chest and upper limbs.

NS was first described by Burkley in 1842 as evenly pigmented patches and Ito and Hamado in 1952 were the first to apply the term NS to speckled lesions.

For a long time, NS was believed to be a benign lesion. However, more than one case of melanoma arising in NS has been published.

As a rule, NS is not considered a precursor of melanoma, but to this day, despite the wide range of publications, it is still necessary to clarify the relationship between NS and melanoma, in terms of the risk factors of turning malignant.

We will describe the clinical features, the evolution and the management of NS, in view also of the recent genetic findings.

Since Burkley first adopted the term Nevus spilus (NS) in 1842, then, many terms have been used as synonyms in the literature to indicate this lesion; speckled nevus: nevus on nevus, naevus sur naevus, spotty nevus, speckled lentiginous nevus, speckled zostriform lentiginous nevus, speckled nevus spilus, café au lait spot and partial unilateral lentiginosis.

NS refers to a more or less circular shaped lesion, a tan to light brown patch of various sizes and sites, either congenital or acquired and characterized by multiple small darker brown macules superimposed, which can be flat or raised and irregular in nature (Figure 1).

The histological patterns of the colored base are those of a simple freckle (macula) or café-au-lait patch, whilst the spotted lesions are usually made up of junctional, compound, or intradermal nevi.

As a rule, NS is not considered a precursor of melanoma, but more than one case has been reported of melanoma arising in NS [1-31].

We will analyze the clinical characteristics and the general evolution of NS and the risk factors of turning malignant.



Figure 1: The classic aspect of nevus spilus (brown patch and darker macules within).



Figure 2: A hybrid form with characteristics between NS and congenital nevus.

Clinical Features

In 1842 Burkley [32] was the first to use the term NS to indicate flat, oval shaped, evenly pigmented patches. The term was subsequently adopted by Kaposi in 1887 [33] and later by Besnier, Brocq and Jacquet [34] in 1902. However, in 1952 Ito and Hamada [35] were the first to use the term NS to refer to a speckled lesion, a hyper-pigmented patch characterized by the presence of small but darker macules within.

NS is a relatively common health condition whose prevalence varies from between 0.2 to 2.3% according to the age groups taken into consideration; the prevalence is similar to the occurrence of a congenital nevus among the general public [36-42].

The question whether NS is a congenital or acquired lesion remains controversial to this day.

According to some authors [43-46], NS, even if not immediately present at birth, it needs to be considered a congenital lesion, or one with close links to a congenital nevus.

There is evidence to suggest that there is a continuity line between the two lesions, with reports about hybrid forms (Figure 2), that



Figure 3: A zosteriform nevus spilus.



Figure 4: Segmental nevus spilus, involving the right part of the face.

demonstrate clinical aspects between NS and congenital nevus [45-46].

The frequency of NS increases in early infancy, suggesting that the later forms were acquired prematurely as the number of NS does not generally increase after the age of nine.

The development of NS starts at birth as a hyper-pigmented patch (café-au-lait spot), and, according to River [37], reaches its peak in number between the ages of five and nine, while it reaches its characteristic speckled aspect between the ages of six and thirty-nine.

Many lesions will have disappeared between the ages of 31 and 60, which have led Kopf [39] to suggest that some forms of NS may regress or completely disappear in time, similar to acquired nevi.

There do not seem to be significant differences in predominance between people of either sexes, or among ethnic groups [36-42] even though there tends to be a certain predilection for the Caucasian race. There are also some reports, though not many, on twins.

No link has been shown to a particular phototype or to the number of acquired melanocytic nevi and its risk of arising in NS; however NS appears more commonly in individuals with the presence of pigmentary abnormalities, such as café-au lait-patches [36]. In most cases NS is composed of a single lesion with an average size, according to Kopf et al. [39], of 4.3 cm (\pm 3.5).

Similarly to the acquired nevus, NS can be classified into 3 distinct clinical types [36], in relation to the size and location. NS is considered small if >1.5 cm, medium if it varies from 1.5 to 19.9 cm and large if its diameter exceeds 20 cm [37]. Segmental, zosteriform NS (Figure 3, Figure 4), can exist [48-53] too. The prevalence of the latter in the general population has not as yet been established because, in the literature, only the odd case has been reported.

Rare are the extensive forms [54-57], which may cover one side of the chest extending to an upper limb, but coming to a neat stop mid-line, and even more unusual are the bi-lateral forms involving a large part of the body surface. There are reports of mosaic forms, characterized by a chess board pattern [57], with normal pigmented skin areas alternating with hyper-pigmented or speckled ones.



Figure 5: The blue variant of nevus spilus (tan maculae with blue nevi).

Finally, also another variant of NS has been recently described: nevus spilus-type congenital melanocytic nevus, in which the large pigmented café-au-lait areas have superimposed with multiple lesions that are indistinguishable from medium/large congenital melanocytic nevi [44-47, 58]. The nevi exhibit a large variety of colors and sizes and may continue to develop during a lifetime, in many cases. The café-au-lait background may not appear immediately at birth, but later, and is still usually predictable on the basis of clustering of many CMN in one anatomical area. Smaller separate lesions in the same individual are often clinically indistinguishable from café-au-lait macules and are so faint that they may be not noticed and, are therefore, not easily diagnosed.

NS can be found anywhere on the body but the most common location is on the chest and upper limbs [39]. Even if the location of these lesions may seem random, some authors have discovered the significant tendency of several forms of NS to be along the Blaschko lines, or to correspond with a dermatome [59-61].

The speckles within NS are often macules rather than papules, with a variable number of elements, from 8 to 10, and generally in

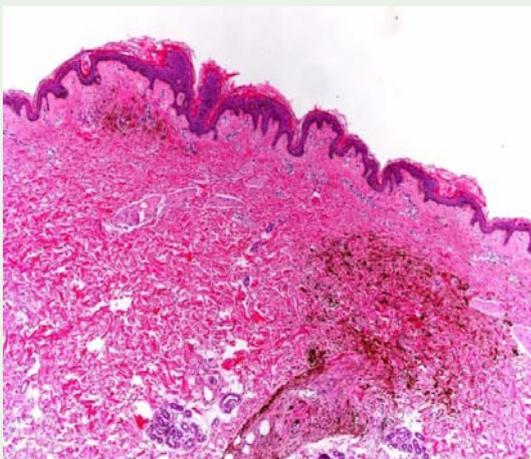


Figure 6: Histopathology of the variant blue of nevus spilus. Two isolated foci of blue nevi associated with hyper pigmentation of in the basal layer of the epidermis. (Hematoxylin-eosin stain; original magnification: x 40).



(a) (b)

Figure 7: A case of segmental neurofibromatosis.

relation to the NS size, even if in some cases, there may be up to 30 elements. The size of these elements varies from 1 to 3 mm [37] but may present a wide variety of dimensions.

Histologically, the hyper-chromatic base of the classic NS shows the histological features of lentigo simplex or a café au lait patch [62].

The increase of pigmentation is in fact linked to a rise in the number of melanocytes in the basal layer, as well as a rise in melanin content of the basal keratinocytes themselves. In addition, there is a moderate acanthosis and elongation of rete ridges.

The speckled lesions can be various types of nevi; junctional, compound, intradermal dysplastic [62], or Spitz nevi [63-66], blue nevi [67-71] (Figure 5, Figure 6), ink spot lentigo [72] and neurotic nevi [73] Rarely, also other non-nevus changes may occur, such as sebaceous hamartoma, hypertrichosis and muscular hyperplasia [74].

NS can also be compared to a melanocytic garden in which a great variety of lesions can grow, among which a melanoma [37, 75]. NS must not be imagined as a static lesion but rather as a dynamic one; the “speckled” lesions can increase in number in time and transform themselves. Different types of lesions may appear on the pigmented base during the different life stages of NS due to various factors such as exposure to the sun, hormonal changes or other causes [36, 61].

NS may present itself either as a single isolated lesion or in conjunction with other skin abnormalities, such as in complex syndromes. In NS syndrome, the skin lesions are linked to ipsilateral dysesthesia, muscular weakness and hyperhidrosis; in phakomatosis pigmentokeratotic, NS is connected to neurological, skeletal or ocular alterations and to epidermal nevi, often of sebaceous differentiation. In type III phakomatosis pigmentovascularis or spilorosea, there is a combination of nevus flammeus and/or anemicus with NS.

Helena Vidaurri-de la Cruz and Happle [76-78] hypothesize about the presence of 2 distinct entities of NS, which are differentiated, according to clinical and histological features for the speckled areas. The macular variety presents itself clinically with flat lesions and histologically with a café-au-lait and lentigo pattern, whilst the papular one often has raised lesions and a histological lentigo, dermal or compound nevus pattern. Both forms can present themselves as isolated anomalies or be part of complex syndromes; the macular form is linked to phakomatosis spilorosea (type III phakomatosis pigmentovascularis) and the papular form is associated with

phakomatosis pigmentokeratolica, an example of didymosis, or NS syndrome [79].

The agminated nevus [80] needs to be considered first of all in the differential diagnosis of NS, where agminated means aggregated, which distinguishes itself by the absence of a pigmented base and is characterized by the presence of localized clustered nevi. Other conditions are café au lait patches, segmental neurofibromatosis (Figure 7), LEOPARD syndrome, Becker nevus and pigmented spots in Albright's disease.

About the origin, NS and also congenital nevus are postulated to result from a post zygotic genetic alteration of the melanocytic lineage, which gives rise to a clone of melanocytes predisposed to developing neoplasm [44]. In a recent publication, Sarin et al. [50] first of all, using exome sequencing, identified an activating clonal point mutation in HRAS (c.37G->C, p.Gly13Arg) in an agminated Spitz nevi arising in a nevus spilus. The HRAS gene belongs to a RAS family of oncogenes that is involved predominantly in regulating cell division. Through the activation of mitogen-activated protein kinase (MAPK) signal-transduction pathway, HRAS promotes cell growth providing instructions in regulating cell division, differentiation, survival and cell death (apoptosis). When mutated, this oncogene has the potential to cause normal cells to become cancerous [81].

In the next publication [51], the same authors identify the presence of the same HRAS mutation in eight additional sporadic NS, suggesting that the HRAS mutation is the predominant causative mutation for NS, and demonstrate that this mutation is sufficient to cause activation of the MAPK pathway. These findings allow us to add NS to the spectrum of congenital lesions that have activating mutation in HRAS.

The authors speculate that in NS the diverse spectrum of melanocytic neoplasm, which take their origin from the tan patches, likely acquire an additional genetic alteration that enables progression but the secondary mutation has not yet been identified.

Progression / Development

As yet, there are no perspective studies available regarding the link between NS and melanoma, nor are there any fixed criteria to establish with reliability which features NS must have to be a potential precursor of melanoma.

From the published studies, the risk of malignant change appears to vary from 0.13% to 0.2% [83-84], and seems higher than for congenital melanocytic nevus.

As a matter of fact, from [84] reported, there is about only one case of melanoma arising in congenital nevus and 3 cases of melanoma in NS in a case study of 150 annual reports of melanoma over a period of more than 15 years of observation.

For years, NS has been wrongly considered a benign lesion and even if NS is not usually a precursor of melanoma, its possible malignant change has been widely reported.

In 1957, the first case of melanoma arising on NS in a patient with neurofibromatosis was published by Perkinson [1]. A further case was described by Beilach [2] in 1984 on a poster presented at the Dermatology Days in Paris and, from then on, 40 more cases of melanoma on NS have appeared in the literature [3-31].

In another study Abecassis et al. [22] re-examined all available case reports, searching for the features that the cases of NS which evolved into melanoma had in common. The first fact that emerged from their study was that the Caucasian, followed by the Black race, were the ones predominantly affected in comparison with the Asiatic race; only one case report was of a Japanese person.

NS tends to appear mainly on the trunk (64%) or upper limbs (36%). Women are generally more affected than men, 56% against 44%. The average age is 49 (median 53), extreme values were represented by a 17-year old being the youngest and an 80-year old being the oldest.

There were 2 cases out of 25 of melanoma arising on NS. In 52% of the cases, melanoma had arisen in lesions already present at birth, in 33% in lesions acquired during infancy and in 14% in lesions that had appeared at the age of twenty or later, and in 4 cases the exact data had not been established. In 60% of the cases, melanoma had arisen in small to medium sized NS, with an average value of 7.4 cm (extreme values 1.5-17cm), in 24% of the cases in zosteriform NS, and in the remaining 16% of the cases, in giant types of NS.

Given the scant number of giant NS, this data confirms the bigger progressive risk these lesions may present.

The type of melanoma most frequently discovered was a superficially spreading melanoma (68%), followed by nodular melanoma (16%), whilst in a few cases a melanoma in situ. The average value of the Breslow thickness was 1.92 mm (median 1.25), fluctuating between 0.27 and 8 mm, but in 5 cases it had not been calculated.

In about 32% of the cases of melanoma in NS, the presence of dysplasia within NS was found during the histological test, but the significance of this fact has not yet been determined.

Even today, we do not know for certain to what extent the surface of the lesion, the number, the type of speckled lesions or the presence of an atypical cytological picture can be correlated to the risk of developing melanoma.

The current protocol for these lesions is frequent monitoring with possible photographic evidence. The possibility of filing and comparing patients' digital images has led to improved management of these lesions [85-87].

If a lesion appears suspicious due to clinical and/or dermoscopic changes, it's advisable to carry out a selective skin biopsy; the outcome of which will determine whether to proceed with an extensive removal of the lesion or to continue monitoring it.

In the case that a histological test proves to be positive, a complete excision of the whole lesion [88], site and size permitting, needs to be carried out in order to get rid of 'bad ground' and to hunt for multifocality of melanoma.

Considering the risk of malignant transformation of NS, it is extremely important to teach patients and relatives how to identify suspicious clinical signs which may lead to the development of a melanoma [83-85].

However, systematically removing all lesions is not justified, bearing in mind the low incidence of NS degenerating, unless the monitoring of the NS is problematic, either because of its body site or the patient's compliance.

In the case of melanoma arising on NS, the treatment and the prospect are the same as those for a common melanoma and the prognostic factors are also the same, influenced by the Breslow thickness, mitotic index, positive lymph nodes and the presence of visceral metastases.

Finally, we would like to raise another question which has been included in recent publications.

The recent article of Manganoni et al. [89], reported the experience of the Melanoma Unit of the University Hospital of Spedali Civili of Brescia regarding the incidence of NS in their patients with melanoma, who are in the follow-up by the Surgery. The NS was quite uncommon; only 27 of 2134 patients (1%) of Manganoni presented NS. NS was presented in different body regions, and was referred as congenital. All the NS were small except in three cases. In the 27 patients, no NS changed into melanoma. On the basis of this study, Manganoni concluded that patients with melanoma do not present a major risk of melanomas arising on NS.

Manganoni, also, evaluates NS from another point of view and wonders whether the presence of a NS might perhaps represent a risk marker of cutaneous melanoma, opening another interesting field of investigation about NS.

Conclusion

One and a half century has passed since Burkley's [33] first description of NS, but it still remains a complex and fascinating entity, often difficult to place and with not a very clear natural history. Even if it is not known for certain which are the possible interacting factors determining the malignant transformation of some forms of NS, the risk factors seem to increase when the lesion is congenital or acquired in early infancy and when its size is $\geq 4\text{cm}$; also the 'nestling' of different types of lesions in the hyper pigmented patch may play a decisive role.

The possibility to study the genetic basis of NS can help us to understand it better in the future and also represents a unique opportunity to recognize the progression from NS to a nevus or to a melanoma.

However, we cannot forget the role of the dermatologist as regards the management of these lesions, which is to maintain a high level of attention. Regular monitoring of NS is of the utmost importance, even of those with seemingly 'innocent and reassuring' aspects. NS needs to be monitored in order to be caught in time in case there is a possible start of malignant transformation.

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