Blue nevi of internal organs are more similar to the so-called dermal melanocytosis than to cutaneous blue nevi

A. FERNANDEZ-FLORES

Service of Cellular Pathology,
Clinica Ponferrada, Spain

Abstract
In this report, we examine several morphologic aspects of blue nevi of internal organs, and compare them to similar conditions of the skin. From a morphologic point of view, blue nevi of internal organs are more similar to the so-called dermal melanocytoses. Nevertheless, since melanocytoses and blue-nevi seem to have the same benign prognosis, and since blue nevus is a historically consolidated term to refer to pigmented spindle cell lesions of internal organs, a most appropriate term, to refer to the latter, will not be easily accepted in literature.

Keywords: blue nevus, melanocytosis, melanosis.

Introduction
Blue nevi have been described in many internal organs, such as the prostate [1], the parotid gland [2], the uterine cervix [3–10], the endometrium [11] the lymph node capsule [12, 13], the oesophagus [14], and the bronchus [15]. They have also been described in tumors, such as ovarian teratoma [16].

Nevertheless, the concept of “blue nevus” of internal organs is far from unified.

While for some, it refers to pigmented stromal spindle-cell lesions (like in the uterine cervix [9] or in the prostate [17, 37], others have referred to the same condition as to melanosis [19]. But the term melanosis is used by others, only when a deposit of melanin is found in these spindle cells plus in the gland epithelium [20, 21].

However, for others, melanosis refers to melanin found in either glandular or stromal location [22], and still others use both terms (melanosis and blue nevus) interchangeably [23].

On the other hand, the term melanosis is used in other organs (such as the uterine cervix [24], or the oesophagus [25] to describe a condition in which pigmented melanocytes are in the basal layer of the epithelium. While in other organs (such as the salivary gland) when pigmented stromal spindle- and dendritic-shape-cell lesions are found, the condition is named as melanocytosis [26]. Others use the terms melanosis and melanocytosis as synonyms [27].

In many reports [20, 28], as well as in classical text books [19, 24], blue nevi of internal organs is said to have the same appearance as dermal blue nevus do. However, the former are made of spindle cells widely separated from each other, and in that sense, they are more similar to certain types of cutaneous nevi other than blue nevus, such as Ota’s or Ito’s nevi, or even the Mongolian spot, which are sometimes grouped in skin pathology as different from blue nevus, under the term “melanocytosis” [29, 30].

We have reviewed in the literature, the diagnostic differential criteria between blue nevus and dermal melanocytoses, and we have applied those criteria to the morphologic examination of blue nevi, and illustrated the main controversies with examples from our own casuistic.

Material and methods
We have searched in literature for differential diagnostic criteria between dermal blue nevus and cutaneous melanocytosis. We have applied those same diagnostic criteria, to the classification of blue nevi of internal organs.

In order to illustrate the results of this study with practical examples, we have performed morphologic studies in cases from our own archives, including blue nevi from internal organs, dermal blue nevi, and dermal melanocytoses.

Traditional techniques of haematoxylin-eosin have been used, as well as histochemical techniques of Masson trichrome.

Immunohistochemistry has been used in order to illustrate the expression by these lesions of S-100 protein (Rabbit anti-cow antibody, DAKO), and HMB-45 (Monoclonal mouse anti-human antibody against melanosomes, DAKO, clone HMB45).

Results
The so-called blue nevus of internal organs is better described the same way that dermal melanocytoses are usually presented in literature, as “diffuse proliferations of dendritic cells” [30].

When differential diagnosis criteria are applied, the pigmented lesions which are found in the internal
organs seem to be closer to melanocytosis than to dermal blue nevi.

For instance, minimal stromal desmoplasia has been used, as a differential diagnosis criterion between melanocytosis and blue nevus (Figure 1), favoring the latter [30, 31]; but desmoplasia is hardly ever seen in blue nevus of internal organs.

In the latter condition, pigmented cells hardly ever present as compact groups of nevus-cells (Figure 2), which is typical of dermal blue nevus, although sometimes the pigmented cells are distributed as “irregularly clumped bundles of cells” in the prostate [32].

The spindle cell component of blue nevi and melanocytosis is virtually indistinguishable from a cytologic point of view [30], but blue nevi often have a secondary component of plump melanocytes (Figure 3), which is not present in melanocytosis, and is not seen in blue nevi of organs, either.

Some base the differential diagnosis between dermal blue nevus and Ota’s nevus, for instance, on the number of melanocytes, which is higher in the former [33] (That is, blue nevus of internal organs is not usually as dense in melanocytes as dermal blue nevus) (Figure 4A).

Concerning immunohistochemistry, blue nevus of internal organs expresses S-100 protein (Figure 4B) [18, 20, 21, 34], while they do not express HMB-45 [18]. This latter fact is not contrary to the melanocytic origin of blue nevus of internal organs, since, even in dermal lesions, it is common that as melanocytes mature, their expression of HMB-45 fades away [35].

On the contrary, dermal blue nevus usually expresses HMB-45 (Figure 5) [30, 36–38], as dermal melanocytosis usually do too [30, 39].

§ Discussions

At present, the issue on how to properly name the benign pigmented spindle cell lesions of internal organs seems to have more a semantic importance than a clinical one.

The slight morphologic differences between dermal melanocytosis and cutaneous blue nevi, are not completely understood either.

From an embryologic point of view, there seem to be no important developmental differences between blue nevi and melanocytosis, and both are considered hamartomatous lesions [29, 40–42], probably derived from a neural crest, made of cells which have been entrapped during their migration [21, 23, 27, 41, 43, 44, 46, 47].

On the other hand, in terms of prognosis, melanocytosis rarely become malignant [30]. Rare examples of malignancy associated to nevus of Ito or Ota have been reported [48, 49], although some estimate the rate of malignant transformation of Ota’s nevus in 5% [33]. Although the rate of malignant transformation of blue nevus is unknown [31], it is also rare for either ordinary blue or cellular dermal blue nevi [28].

All this is in consonance with the behavior of the so-called blue nevi of internal organs, which rarely (if ever) becomes malignant: very few reports of primary malignant melanoma of the prostate [50, 51], uterine cervix [46, 52–54], or bronchus [55–60], for example, have been presented.

There is, however, no evidence to assume if the preceding lesions, in these malignant cases, were blue nevi, melanoses or melanocytosis [21]. And it has to be taken into account that only melanoma with proved junctional activity are considered as true primary malignant melanoma by some [53] excluding in that way, the cases that could have developed from blue nevi.

In conclusion, blue nevi of internal organs probably should receive another name if we attend to morphological aspects. Nevertheless, the apparently null difference in prognosis between both types of spindle cell lesions, together with the historically consolidated name “blue nevus”, make it most unlikely to have a more suitable term for the entity at present. Maybe in the future we will understand better the nature of these morphologic differences, and a more appropriate designation will be used.

§ Conclusions

The so-called blue nevi of internal organs are closer, from a morphological point of view, to dermal melanocytoses than to dermal blue nevus, if the same morphologic differential criteria that are usually applied in the diagnosis of skin pathology are also used for internal organs (Table 1).

Table 1 – Principal differential diagnostic criteria between dermal blue nevus and dermal melanocytosis. Blue nevus of internal organs shows characteristics which are closer to dermal melanocytosis than to dermal blue nevus.

<table>
<thead>
<tr>
<th>Dermal blue nevus</th>
<th>Dermal melanocytosis</th>
<th>Blue nevus of internal organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmoplasia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Compact groups of pigmented cells</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Secondary component of plump melanocytes</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>S-100</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HMB-45</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

References

Blue nevi of internal organs are more similar to the so-called dermal melanocytosis than to cutaneous blue nevi.

Figure 1 – Desmoplasia in dermal blue nevus: it can vary from mild (A) to strong (B). Desmoplasia is better remarked by Masson's Trichrome stain (C).
Figure 2 – Areas of blue nevus in a teratoma. The pigmented cells show quite a loose pattern, opposite to the compact pattern of dermal blue nevus.

Figure 3 – Plump melanocytes from a dermal blue nevus, which are not found in blue nevus of internal organs.

Figure 4 – Blue nevus of prostate, showing the loose pattern of the cells, even when they are close to each other (A). The immunostain for S-100 was positive (B). This same case did not show any expression of HMB-45.

Figure 5 – Immunostain of dermal blue nevus for S-100 protein (A), and HMB-45 (B).
Blue nevi of internal organs are more similar to the so-called dermal melanocytosis than to cutaneous blue nevi.


**Corresponding author**
Angel Fernandez-Flores, MD, PhD, Servicio de Patología Celular, Avenida Galicia 1, 244 00 Ponferrada, Spain; Phone (00 34) 987–42 37 32, Fax (00 34) 987–42 91 02, E-mail: gpyauflowerlion@terra.es

*Received: January 7th, 2007*

*Accepted: February 10th, 2007*