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COMMON BLUE NEVUS OF THE UTERINE CERVIX: A REPORT OF 16 CASES

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ABSTRACT

Blue nevus is an uncommon pigmented lesion of the skin that rarely appears in the different mucoses, such as cervix or vagina.

Sixteen cases of cervical blue nevi were diagnosed in our department in a five-year period (2000-2004). Localized in the stroma of the cervical canal, predominantly in the posterior lip, the lesions measured 0.1-2cm. Prussian blue stain excluded the presence of hemosiderin and Masson-Fontana, S100 and HMB-45 stains confirmed the melanocytic nature of the lesions.

Our findings are similar to those published in several studies. The recognition of this obscure lesion prevents its misinterpretation as siderosis or malignant melanoma.

Key words: blue nevus, uterine cervix, histochemistry, immunohistochemistry, differential diagnosis

INTRODUCTION

Blue nevus is an uncommon benign pigmented lesion of the skin composed of clusters of melanocytes associated with a variably fibrotic stroma, situated in the dermal connective tissue. These dermal melanocytes appear as either dendritic, spindle, oval or polyhedral cells and are clearly separated from the superficial epidermis [1]. Many of these cells resemble embryonal melanocytes migrating from the neural crest to the skin [2]. Immunophenotypically, the tumor cells usually express HMB-45, in addition to S100 and Mart-1 (melan A) [2].

The common, Jadasssohn-Tieche type, and the cellular type of blue nevus differ in their histological appearance and localization; however, nevi often manifest intermediate features [1,2,3]. Except for the skin, blue nevi also appear at other sites, such as oral mucosa, uterine cervix, vagina, prostate, spermatic cord, pulmonary hilus, sclera, orbit, conjunctiva, breasts and lymph nodes [1,4]. These blue nevi also known as "extracutaneous" are thought to derive from the neural crest as well, but their histogenesis is still controversial [4,5].

Except for the skin of vulva, pigmented lesions are extremely rare in the genital tract [6]. However, benign blue nevi have been reported to occur in the uterine cervix and vagina, too. They were first recognized by Hinselmann in 1942, as "pigmented connective tissue cells in mucosa of endocervical canal of women". Usually situated beneath the endocervical epithelium, they appear as blue-blackish lesions, less than 10 mm in diameter [2,7]. Blue nevi are rarely recognised on gross examination and are therefore most commonly incidental findings in hysterectomy or cone specimens [8,9]. Although considered to be quite rare, they can be detected in up to 28.6% of the female patients, when carefully looked for in surgical cervical specimens [8].

The aim of this study is to present sixteen cases of benign blue nevi of the uterine cervix. Their macroscopic, cytological, histochemical and immunohistochemical features are shown in this study as well, in comparison to similar findings in the literature.

MATERIALS AND METHODS

According to the computer database of the Department of Histopathology and Clinical Cytology at the Institute of Radiotherapy and Oncology in Skopje, a total of sixteen cases of benign blue nevi of the uterine cervix were diagnosed during a five-year period (2000-2004) and were included in this retrospective study. Fifteen of the cases were diagnosed in the 5917 hysterectomy (3924) and cone (1993) specimens examined during this period, whereas

only one case was diagnosed in a curettage specimen.

The important clinical data for the patients are shown in table 1. The patients were treated according to the clinical diagnosis, as shown in the same table (Table 1).

PAP smears were taken in fourteen of the sixteen patients prior to the surgical treatment or explorative curettage.

All surgical specimens were fixed in 10% buffered formaldehyde for 24 hours, and biopsy specimens were fixed for a minimum of 6 hours. The surgical specimens were routinely examined and sections taken according to the standard procedure for gynecologic specimens. Two sections from the uterine cervix were taken from the surgical specimens removed for uterine prolaps, leiomyomas or ovarian tumors, whereas at least thirteen sections from the cervix were taken from the specimens with CIN (cervical intraepithelial neoplasia) lesions. Subsequently, sections were routinely processed and paraffin embedded. 5μ thin sections were cut and placed on pretreated slides. Apart from the standard hematoxylin-eosin stain, additional histochemical (Prussian blue for iron, Masson-Fontana for melanin) and immunohistochemical stains (HMB-45 and S100) were performed.

For the immunohistochemistry, epitope retrieval step was performed in a microwave oven (400W) using citrate buffer for a period of 30 minutes. Primary antibodies were obtained from Dako Cytomation, Glostrup, Denmark. For the HMB-45 antibody (anti human melanosome, clone HMB45[1]), dilution 1:50 gave optimal results, whereas for the S100 antibody (polyclonal, rabbit, anti S100) the optimal dilution was 1:3000. Both antibodies were incubated at room temperature for one hour. Visualisation of the conjugated primary antibodies was achieved using standard streptavidin-biotin-avidin peroxidase complex (Vectastain universal elite ABC kit, Vector Laboratories, Inc. USA). Subsequently, 3.3'-diaminobenzidine (DAB) was used as chromogen and the slides were finally counterstained with hematoxylin.

RESULTS

The age of the patients ranged between 41 and 71 years (mean, 49.6±7.6, Table 1). Clinical suspicion of blue nevus or any kind of pigmented lesion of the uterine cervix was not raised in any of the sixteen cases. They were all incidental findings identified during the histopathological evaluation of the specimens. A pigmented lesion of the uterine cervix was grossly visible in only one case, in a uterus removed for leiomyomas (Table 1, case 15, Fig. 1a). A dark grey to black coloured tumor 0.9 cm in diameter was localised in the posterior lip of the cervical canal, causing only minor protrusion (less than 0.2 cm) above the mucosal surface. In the remaining fourteen surgical specimens pigmented lesions were not visible on gross inspection.

All PAP smears taken in fourteen of the patients were negative regarding the presence of pigmented cells. Nevertheless, in three cases cytological abnormalities of the cervical squamous epithelium were found (cases 3, 10, 12, Table 1).

The histopathological findings in relation to the initial clinically apparent disease are listed in Table 2 and are concordant with the clinical diagnosis in general.

The blue nevi were localized at the posterior cervical lip in four patients (cases 1, 6, 7, 15, Table 2), at the anterior lip in two patients (cases 3, 12, Table 2) or involved the whole circumference of the canal in one patient (case 10, Table 2). In the remaining eight surgically treated patients, topographic data regarding the blue nevi were missing (cases 4, 5, 8, 9, 11, 13, 14, 16, Table 2).

In the fifteen surgical specimens, blue nevi were situated proximally from the external uterine orifice in the cervical canal at a distance ranging between 0.1 and 1.9 cm (Fig. 1a, case 15, Table 2). The maximal diameter of the sixteen lesions ranged from 0.1 to 2 cm, whereas the depth of the lesions varied from 0.1 to 0.4 cm (Table 2).

The histological appearance of the blue nevi was similar in all sixteen cases. They all consisted of spindle, dendritic or oval melanocytes located in the endocervix, in the stroma beneath the mucosal surface. The nuclei of the cells were small, round to oval, while the cytoplasm contained variable fine delicate pigmentation and formed slender elongated processes (Fig. 1b, case 15, Table 1&2). Mitotic figures and atypical cells were virtually absent. Apparently, the longitudinal axis of many melanocytes was parallel to the surface epithelium and clusters of cells surrounded

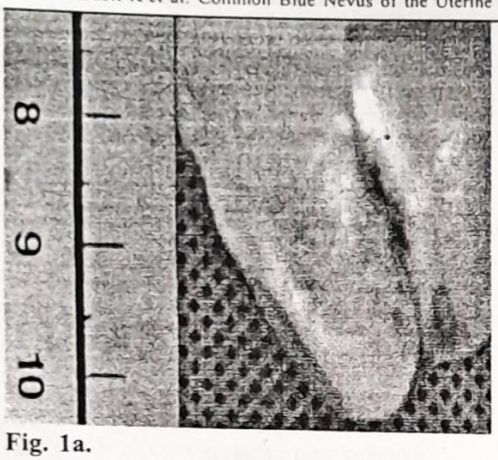


Fig. 1a.

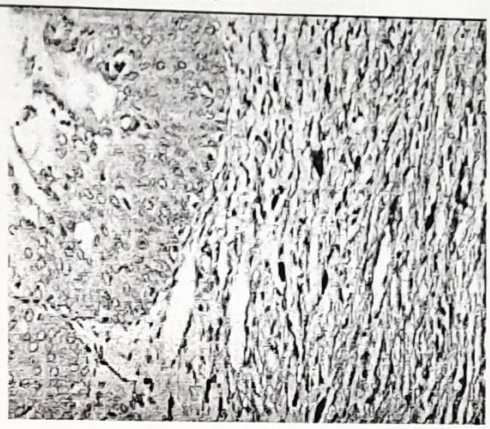


Fig. 1b.

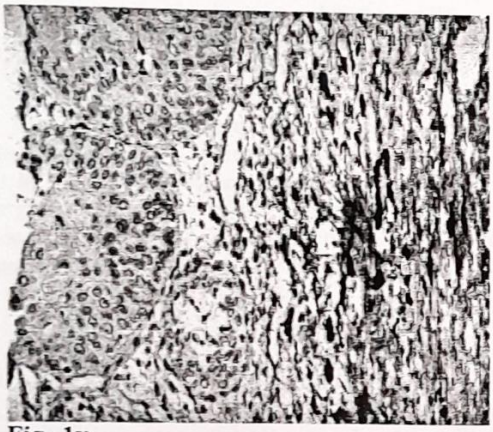


Fig. 1v.

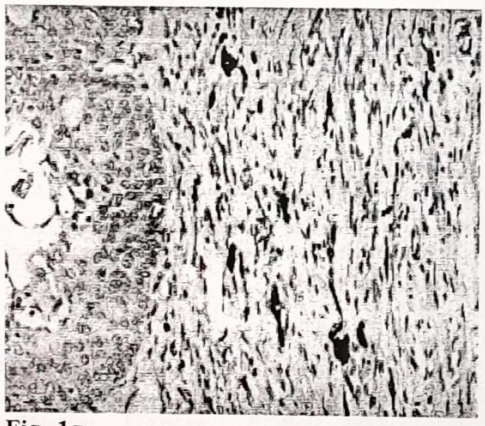
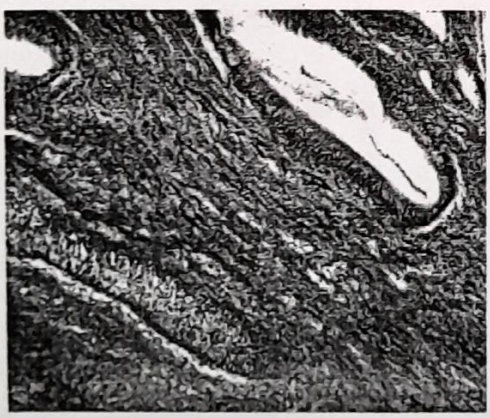


Fig. 1g.

Fig. 1. Case 15 (a) Gross and (b) histological appearance of a blue nevus at the posterior lip of the uterine cervix (hematoxylin-eosin staining, original magnification, x 200) (v) HMB-45 immunohistochemical staing staining for confirmation of melanosomes (original magnification, x 200) (g) S100 immuno-histochemical staing for confirmation of neurogenic origin of the cellls (original magnification, x200).



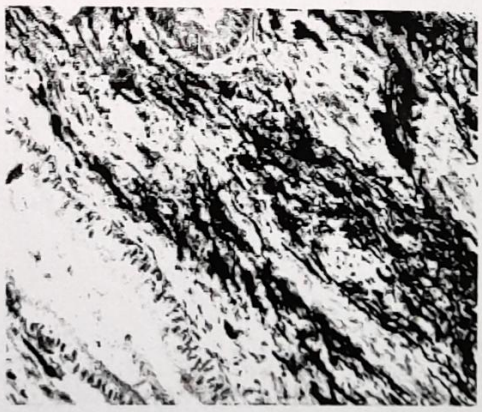


Fig. 2. Case 8 (a) Histological appearance of a blue nevus of the uterine cervix (hematoxylin-eosin staining, original magnification, x100) (b) Masson-Fontana staining for confirmation of melanin granules (original magnification, x200).

Table 1. Clinical characteristics of the sixteen patients with blue nevi of the uterine cervix.

No	Age	Clinical finding	Treatment
1	48	Uterus myomatosus, CIN 1	HTA cum BSO
2	52	Metrorrhagia, Hyperplasia endometrii	Curettage explorativa fractionata
3	45	CIN 2, HPV 56	Conisatio
4	59	Prolapsus uteri	HTV cum BSO
5	50	Uterus myomatosus	HTA cum BSO
6	71	Tumor cysticum adnexae lateris sinistri	HTA cum BSO
7	41	Uterus myomatosus	HTA sine BSO
8	46	Uterus myomatosus	HTA cum BSO
9	46	Uterus myomatosus	HTA cum BSO
10	41	Carcinoma planocellulare cervicis uteri, FIGO stage IIA	HTR cum BSO & RL (sec. Wertheim- Meigs)
11	46	Uterus myomatosus	HTA sine adnexectomia
12	45	CIN 3	HTA cum BSO
13	48	Block tumor in cavi pelvicis, PID	HTA cum BSO
14	55	Uterus myomatosus	HTA cum adnexectomia lat. Dex.
15	45	Uterus myomatosus	HTA sine adnexectomia
16	56	Uterus myomatosus	HTA cum BSO

Legend: : No, patient's number; CIN, cervical intraepithelial neoplasia; PID, pelvic inflammatory disease; HTA, total abdominal hysterectomy; HTR, total radical hysterectomy; RL, regional lymphadenectomy, BSO- bilateral salpingo-oophorectomy.

Table 2. Morphological characteristics of the sixteen patients with blue nevi of the uterine cervix.

No	PAP	Histopathologic finding	Local	Diamet	Masson-Fonatana	Prussian blue	HMB-45	S100
1	1	Leiomyomata corporis uteri/ Dysplasia epithelii cervicis uteri gradus levis	PL	0.6	+	-	+	+
2	1	Hyperplasia simplex endometrii	UK	1	+	-	+	+
3	1	Dysplasia epithelii cervicis uteri gradus levis	AL	0.5	+	-	+	+
4	1	Cervicitis chronica	UK	0.9	+	-	+	+
5	1	Leiomyomata corporis uteri	UK	0.8	+	-	+	+
6	1	Cystis paraovarialis torquata	PL	0.6	+	-	+	+
7	1	Leiomyomata corporis uteri	PL	0.1	+	-	+	+
8	1	Leiomyomata corporis uteri	UK	2	+	-	+	+
9	1	Leiomyomata corporis uteri	UK	1.5	+	-	+	+
10	1	Carcinoma planocellulare cervicis uteri	A&PL	1.1	+	-	+	+
11	1	Leiomyomata corporis uteri	UK	0.4	+	-	+	+
12	1	Dysplasia epithelii cervicis uteri gradus gravis	AL	0.4	+	-	+	+
13	1	Cystis corporis lutei	UK	0.2	+	-	+	+
14	0	Leiomyomata corporis uteri	UK	0.1	+	-	+	+
15	1	Leiomyomata corporis uteri	PL	0.9	+	-	+	+
16	0	Leiomyomata corporis uteri	UK	0.1	+	-	+	+

Legend: No, patient's number, PAP, PAP test: 1- Pap smear negative regarding the blue nevus, 0- no PAP smear was taken prior to the intervention; Local, localization in the uterine cervix; AL, anterior lip; PL, posterior lip; UK, unknown; Diamet, diameter in cm..

endocervical glands (Fig. 2a, case 8, Table 1&2). The superficial epithelium did not show proliferation of melanocytes or contain melanin pigmentation. In all sixteen lesions Prussian blue stain for iron gave negative results, therefore excluding the presence of hemosiderin granules (Table 2). Masson-Fontana stain confirmed the brown pigment to be melanin (Fig. 2b, case 8, Table 2). Positive results in all sixteen cases were also obtained by immunohistochemistry, using antibodies against HMB-45 antigen (Fig. 1v, case 15, Table 2) and S100 protein (Fig. 1g, case 15, Table 1).

DISCUSSION

The blue nevus is a benign tumor appearing generally in the skin and rarely in the different mucoses. Its morphological description in the skin was first given by Tieche ninety- nine years ago, but its recognition as a uterine cervical tumor happened almost forty years later [2].

Even after half a century from its recognition, the histogenesis of the cervical blue nevus is still controversial. Embryologically, dendritic melanocytes are considered to derive from the neural crests [2,4,5,10,11], but some authors emphasize the possibility of local differentiation of preexisting cells [9]. For example, in the 60s and 70s of the last century Cid favored the neural derivation and Schwannian origin of melanocytic cells. He also first described that scattered melanocytes could be found in 3.6% of uterine cervices [9,11-13]. Conversely, his opinion was not shared by Goldman, who preferred the Mullerian origin of melanocytes, supporting his hypothesis by the fact that these cells could undergo decidual transformation [9,14,15]. However, latest publications on this topic are in favor of neural derivation of melanocytes [2].

More than 120 cases of cervical blue nevi have been reported in the literature [4]. Blue nevi could be found in up to 8.6% of hysterectomy specimens when only one section of the uterine cervix was taken [16]. However, when step sections were taken, foci of melanocytes were identified in up to 28.6% of the cases [8]. In our study, blue nevi of the uterine cervix were detected in only 0.25% (15/5917) of the hysterectomy or cone specimens. This relatively low incidence is consistent with the reports of several authors [10,14,16]. For instance, the incidence of cervical blue nevi in Bhagavan's study of 2.500 hysterectomy specimens was 0.12%. Similar findings were reported by Cid, who found 9 (1.9%) cases of blue nevi among 466 cervices [8]. The differences in the macroscopic dissection of the specimens and histochemical stains used might cause this discrepancy. For example, the incidence of blue nevi is higher in the studies where Masson-Fontana stain was performed initially on each section from the cervix [8]. Additionally, when sections are taken only from the distal portion of the cervix, blue nevi could be missed due to their deep endocervical localization. The higher incidence of blue nevi reported in Japanese studies may also be related to the racial or ethnic differences in the incidence of the pigmented lesions in general [8,16].

Blue nevi are considered to be acquired lesions that develop during many years. Some authors even speculate that they might be related to hormonal disturbances in the menopause [16]. Hence, cervical blue nevi are more prevalent in the middle-aged to elderly women [4,8]. According to the Japanese study of 54 cases, the peak incidence of the blue nevi is in the sixth decade of life [8]. Our sixteen cases of blue nevi were all detected in middle-aged to elderly women; however, more than a half of them were in their fifth decade of life (62.5%).

Common blue nevus of the uterine cervix is considered an incidental finding, usually in uteri removed for leiomyomas [4,17]. In the Japanese study of 189 hysterectomy specimens, stromal melanocytic foci were found equally frequently in the uteri removed for leiomyomas or adenomyosis [8]. In our study, 53.3% of the uteri with blue nevi were removed for leiomyomas. This phenomenon, however, could be explained with a high incidence of leiomyomas in women in general. Only rare cases of cervical blue nevi have been detected in curettage or biopsy specimens. To our knowledge, the three cases of blue nevi discovered in a biopsy, polypectomy or curettage material were published by Waxman in 1973, Hernandez in 1976 and Quizilbach in 1977 [5,20]. Consistent with these findings, only one of our cases was identified in a curettage specimen.

There are various publications regarding the localization of the blue nevi. All authors agree

upon the endocervical localization of the blue nevus, but some favor the anterior and others posterior lip of the uterine cervix [8,15,16,18]. In the Japanese study of Uehara et al. 1991, 42/486 cases of so-called "stromal melanocytic foci" were detected in the cervices, when only sections from the posterior lip were taken. However, the same author later that year reported predominant occurrence of the "stromal melanocytic foci" in the anterior cervical lip (54%, 29/54) [8,16]. On the contrary, in our study blue nevi were more frequent in the posterior than in the anterior lip of the uterine cervix; it should be noted, however, that topographic data were available in only 7 cases.

The usual endocervical localization of the blue nevi renders them invisible on colposcopic examination. The sixteen cases included in our study were localized in the cervical canal, at a distance ranging from 0.1 to 1.9 cm proximally from the external uterine orifice, consistent with other topographic reports on blue nevi [8,15-17,19]. Moreover, they are easily overlooked on gross examination of the surgical specimens by the pathologists because of their endocervical localization, resemblance to haematoma and small dimensions [7]. Hence, in our study none of the cases had been previously recognized by the clinicians. The only grossly visible blue nevus in one of the hysterectomy cases measured 1 cm. Our findings are similar to the ones reported by Uehara et al. in 1991. In that study, only one of the 42 cases of stromal melanocytic foci was grossly visible [16].

The stromal localization of the melanocytes makes them virtually undetectable by exfoliative cytology [7-9,13], which was also the case in our study. Accordingly, the PAP smears taken in fourteen of the cases were negative regarding the presence of pigmented cells.

Fourteen years ago, Uehara recommended that blue nevus of the uterine cervix as a term ought to be reserved for larger lesions, whereas small clusters of melanocytes in the uterine cervix should be called "stromal melanocytic foci", since they resemble dermal melanocytosis [16]. So far, his point of view is not widely accepted or discussed in the literature. Therefore, even small lesions measuring less than 0.1 cm are considered as blue nevi. The mean diameter of this lesion is 0.4cm [7], but cases ranging from 0.1 to 1.3 cm in diameter have also been described [17,19]. To our knowledge, the largest ever reported cervical blue nevus measuring 3 cm was described by Zevallos-Giampietri in 2004 [4]. The sixteen cases included in our study measured within the expected range between 0.1 and 2 cm in diameter.

The blue nevi of the uterine cervix share a common histological picture with the familiar cutaneous blue nevus. The same bipolar or branching dendritic processes can be found in both lesions. Fine, abundant granular brown pigment is observed in the cytoplasm of melanocytes, which gives a positive histochemical reaction of melanin. In contrast, melanophages contain larger pigmented granules and do not contain dendritic processes [10,14,20]. However, an inexperienced pathologist might interpret the foci of melanocytes as hemosiderosis. For example, in the study of three cases of Goldman et al. 1967, two had been previously misinterpreted as siderosis [10]. We agree with the suggestion given by many authors that easy to perform histochemical stains for iron (Prussian blue) and melanin (Masson-Fontana) can be quite helpful in solving the possible dilemma [10,21]. The blue nevus melanocytes strongly express HMB-45, in addition to S100 and Mart-1 (melan A) [2,22]. HMB-45 reacts with neuraminidase sensitive oligosaccharide side chain of a glycoconjugate present in immature melanosomes. The polyclonal S100 antibody reacts with low molecular weight calcium binding protein expressed in glial cells and melanocytes. The lower S100 expression of melanocytes is probably related to the inverse correlation of the S100 positivity and pigment load [23]. Immunostains could also highlight obscure dendritic cells not loaded with melanin pigment. Consistent with these observations, the sixteen cases included in our study strongly expressed HMB-45 as well as S100 protein, along with a positive histochemical staining for melanin granules (Masson-Fontana stain). Mart-1 immunostain was not performed on our cases, since it was not available in our Department.

The presence of blue nevi in the uterine cervix, prostate and other visceral organs could explain the origin of some puzzling malignant melanomas that occur in visceral organs without previous cutaneous manifestation [8]. However,

according to the literature, cellular or atypical blue nevi have never been described in the uterine cervix, and the common blue nevus is not considered a precursor lesion [4]. Strict criteria have been proposed for the diagnosis of primary malignant melanoma of the uterine cervix, one of which is evidence of junctional activity of melanocytic cells in the adjacent epithelium. Additional, but equally important criteria include absence of cutaneous lesion, presence of melanin granules and characteristic pattern of spread for primary cervical or vaginal malignant neoplasms [9,11]. Following these criteria, less than 50 cases of primary malignant melanoma of the uterine cervix have been published [4], including the one from our Department published four years ago [11-13,21,24-28]. None of these cases was associated with the presence of a blue nevus.

Other pigmented lesions, such as melanosis, lentiginous melanocytic lesions or pigmented melanocytic schwannoma of the uterine cervix may also be included in the differential diagnosis of a blue nevus [4,29]. Nevertheless, the distinction between these entities is usually straightforward.

Blue nevi have been described in the vagina as well [30]. In this localization, they are equally rare and usually clinically misdiagnosed as malignant melanomas. For example, Tobon et al. in 1977 described one case of blue nevus of the vagina in a postmenopausal woman, with previous clinical suspicion of malignant melanoma.

In conclusion, benign blue nevi of the uterine cervix are not as rare as previously thought [4], and stromal melanocytic foci can be detected in up to 28.6% of the cervices when step sections are taken. The importance of the recognition of this obscure asymptomatic lesion lies in the possibility of its misinterpretation as siderosis or malignant melanoma. Careful macroscopic and histological examination of the surgical uterine or cone specimens is mandatory for the recognition of this pigmented lesion. The distinction between the blue nevus and the similarly appearing siderosis is quite easy, and can accurately be achieved using two easy to perform histochemical stains. Additional immunohistochemical stains, such as HMB-45 and S100 can also be used in order to visualise obscured dendritic cells.

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