

## Foci of stromal melanocytes (so-called blue naevus) of the uterine cervix in Japanese women

Toshitaka Uehara<sup>1</sup>, Shojiro Takayama<sup>1</sup>, Tamiko Takemura<sup>2</sup>, and Tsutomu Kasuga<sup>3</sup>

<sup>1</sup> Department of Pathology, Research Institute, Saitama Cancer Center, Ina-machi, Saitama-ken 362, Japan

<sup>2</sup> Department of Pathology, Japan Red Cross Medical Center, 4-1-22, Hiroo, Shibuya-ku, Tokyo 150, Japan

<sup>3</sup> Second Department of Pathology, Faculty of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan

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**Summary.** Foci of stromal melanocytes (FSM) of the uterine cervix have been known as extra-cutaneous “blue naevus”. However macroscopic and histological findings suggest that FSM of the cervix are analogous to dermal melanocytosis, rather than to cutaneous blue naevus and the lesions are more appropriately called stromal melanocytosis. FSM of the cervix have been considered rare, but our study showed that they are not uncommon in Japanese women occurring in 8.6% (42/486). The lesions were initially observed in the third decade of life and became most prevalent in the fifth decade (15/86 cases, 17.4%). In stroma of the cervix, stromal melanocytes (SM) were present where many peripheral nerve fibres were seen. SM of the cervix were positive for S-100 protein in immunohistochemical studies and were sometimes observed close to peripheral nerve fibres. Melanocytes were never observed in the ectocervical and endocervical epithelium, but only in the stroma of the cervix. We suggest that malignant melanoma of the uterine cervix may originate from SM.

**Key words:** Melanocytes – Blue naevus – Stromal melanocyte – Stromal melanocytosis – Uterine cervix

### Introduction

Foci of stromal melanocytes (FSM) of the cervix were first described as “pigmented connective tissue cells in mucosa of the endocervical canal of women” (Hinselmann 1942). These lesions are now known as “blue naevus of the uterine cervix”. Approximately 50 cases have been reported to date (Cid 1959; Patel and Bhagavan 1985; Matsumoto et al. 1989) and we have identified 42 cases during the 4 years from 1983 to 1986. FSM are believed to be analogous to cutaneous blue naevus (Cid 1960; Goldman and Friedman 1967; Qizilbash 1973). However, we believe that these lesions are analo-

gous to dermal melanocytosis rather than to cutaneous blue naevus.

In this paper, we attempt to determine the incidence and histogenesis of melanocytes of the cervix using the uteri of 486 randomly selected Japanese women. We discuss the difference between stromal melanocytosis and blue naevus of the cervix and consider the possible histogenesis of malignant melanoma of the cervix.

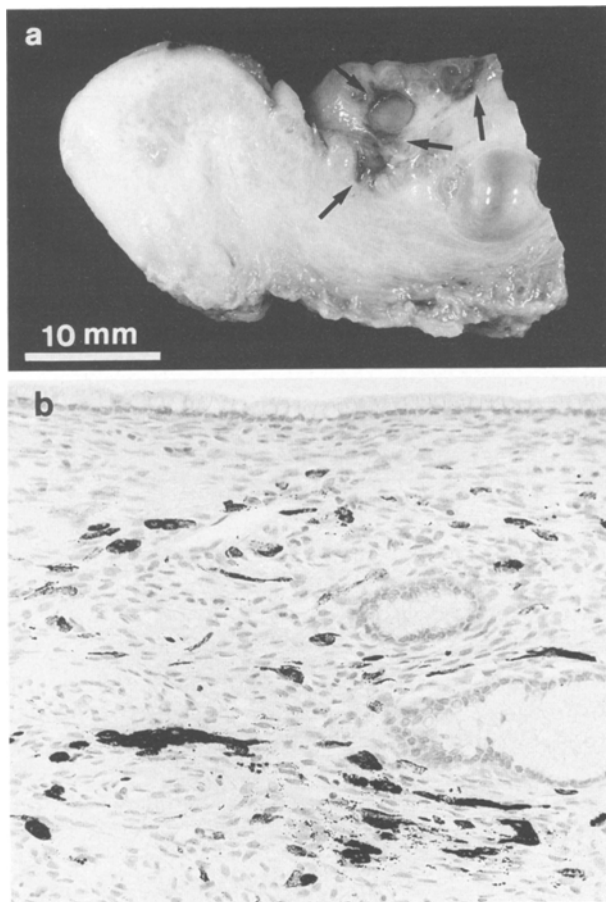
### Materials and methods

A total of 486 uterine specimens were studied, consisting of autopsy specimens (199 cases) and surgical specimens (287 cases). Most of the autopsy cases had malignant lesions such as gastric, colonic or lung carcinoma. The surgical cases consisted of leiomyoma (197 cases), adenomyosis (42 cases) and non-neoplastic disease (48 cases) such as prolapse and endometriotic ovarian cysts. Specimens with carcinoma of the uterus were excluded. The age of the autopsy cases ranged from newborn to 86 years with a mean age of  $53 \pm 21$  years. The ages of the surgical cases ranged from 29 to 79 years, with a mean age of  $45 \pm 6$  years.

The uterine specimens were prepared with 10-fold buffered formalin solution (3.8%). A sagittal cross-sectional specimen of the posterior wall was removed from each uterus, and was cut into three to five blocks, embedded in paraffin, cut into thin sections of 3–4  $\mu\text{m}$ , and stained with haematoxylin and eosin. To confirm the presence of melanin granules, specimens were also stained using Grimelius and Masson-Fontana techniques. Haemosiderin granules were excluded using Berlin-blue stain. Specimens containing melanocytes were examined by an indirect immunoperoxidase (PAP) technique using polyclonal rabbit anti-cow serum specific for S-100 protein (Dako, Carpinteria, CA). In three surgical cases containing melanocytes, tissue blocks taken from formalin-fixed specimens were processed for electron microscopy and examined with a Hitachi H-500.

### Results

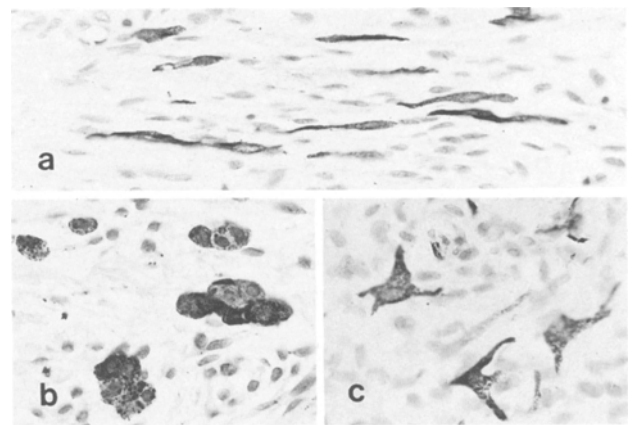
Forty-two out of 486 cases were positive for melanocytes in stroma of the cervix, 41 of which were determined using microscopic examination. The remaining case was a 51-year-old female who underwent surgical removal



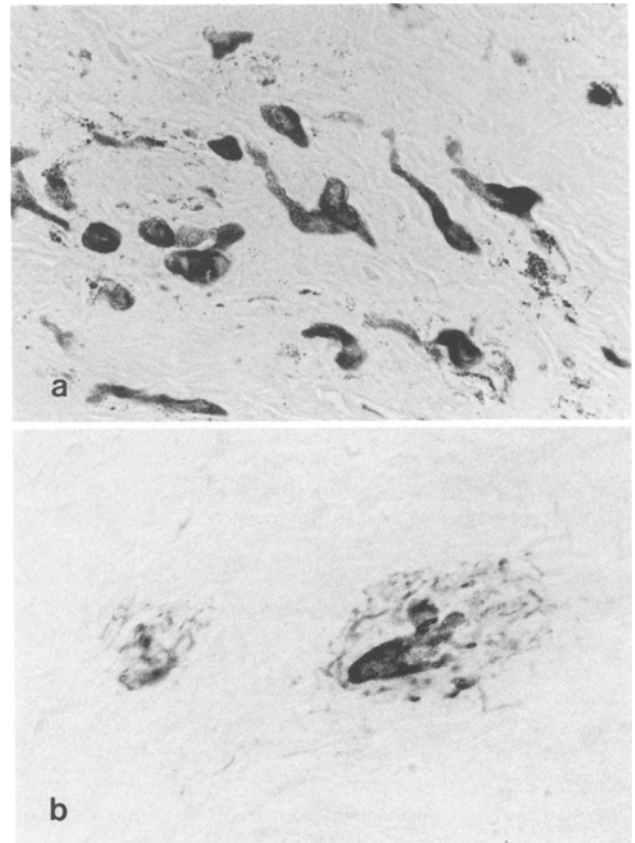
**Fig. 1. a** A case of foci of stromal melanocytes (FSM) of the uterine cervix in a 51-year-old female with leiomyoma of the corpus. Cut surface of the cervix shows four irregularly shaped dark brownish pigmented areas, as large as  $5 \times 2$  mm around the dilated cervical glands (arrow). Note absence of nodule formation. **b** Same case as in **a**. Scattered distribution of stromal melanocytes (SM) around the cervical glands. Melanin pigments are stained a blackish colour. Note absence of expansive growth into the cervical glands or surface epithelium. Masson Fontana method,  $\times 385$

of the leiomyoma of the uterine corpus, and in whom a brown melanin-like pigmentation could be seen grossly in the cervix. On cut section, macroscopically discrete brown spots were found in the cervical stroma around the dilated cervical glands (Fig. 1a) with no melanocytic nodular lesions protruding into the cervical canal. These discrete melanocytic spots showed neither expansive nor invasive growth into the neighbouring endocervical glands and/or endocervical surface epithelium (Fig. 1b). The cellularity of the previous 41 cases and the latter case was almost identical, but the latter appeared to have melanin granules in each melanocyte in greater numbers than the former. In all 42 cases, melanocytes were distributed in the stroma only, under the endocervical epithelium and around the endocervical glands, but not at the ectocervical and endocervical epithelium, nor in endocervical glands. The endometrium and myometrium were free of melanocytes.

Stromal melanocytes (SM) were scattered in stroma of the cervix. The long axis of their melanocytes was often arranged parallel to the surface epithelium of the

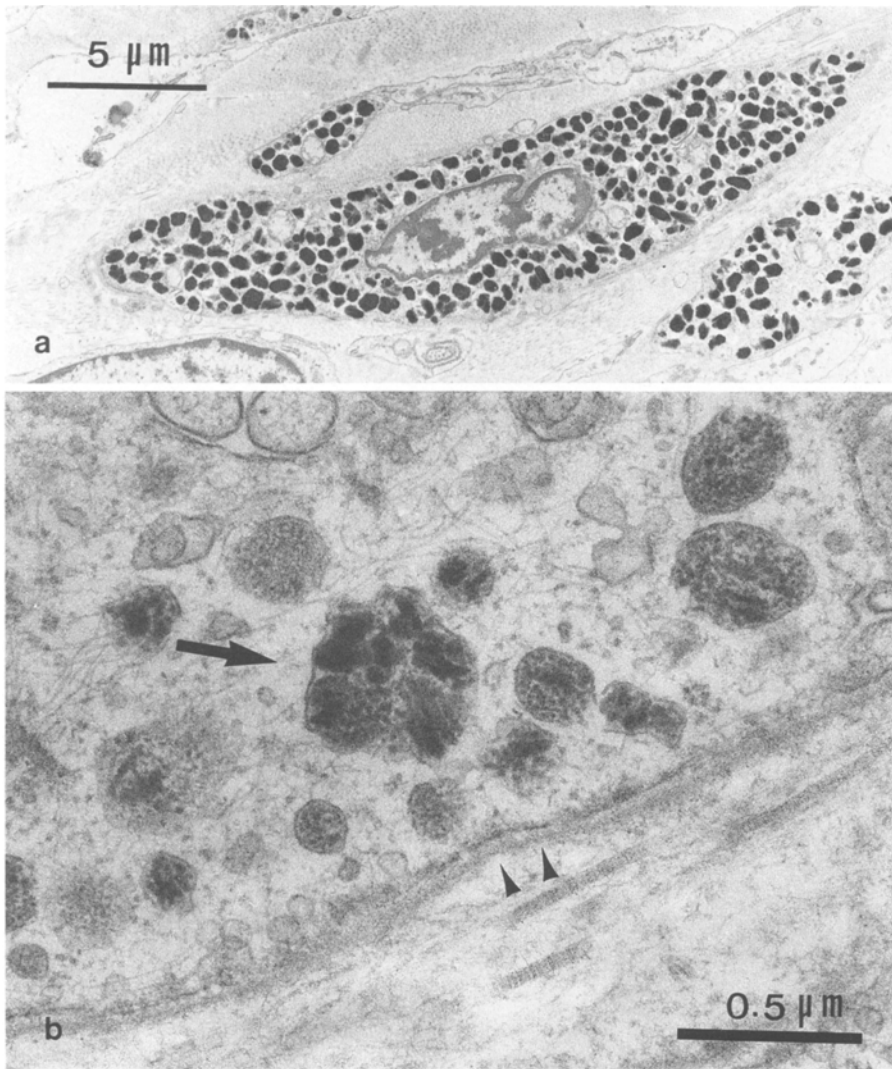


**Fig. 2. a** A case of a female with leiomyoma of the uterine corpus. Histologically, the spindle-shaped SM can be observed, though macroscopically no pigmented lesion of the uterine cervix is found. Masson Fontana method,  $\times 1300$ . **b** In some sections, melanocytes conjugated and transformed to a pattern of naevus cell nests can be observed. Masson Fontana method,  $\times 1800$ . **c** Dendritic-shaped SM can be observed occasionally. Masson Fontana method,  $\times 1800$



**Fig. 3. a** Immunohistochemically, SM show dark brown-coloured cytoplasm because of their melanin granules and S-100 protein. S-100 protein, PAP method,  $\times 3000$ . **b** SM surrounded by the nerve fibre branches reveals dendritic dark brown coloured cytoplasm. S-100 protein, PAP method,  $\times 3000$

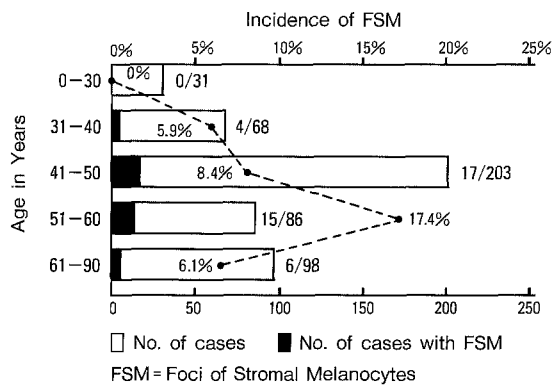
endocervix and followed the orientation of the connective tissue (Fig. 1b). The size and number of FSM were different in each case, that is, most of them ranged from  $50 \times 100 \mu\text{m}$  to  $1 \times 5$  mm in size and were located in one



**Fig. 4. a** A single bipolar melanocyte in the stroma is shown.  $\times 4000$ . **b** High magnification of SM, demonstrating basement membrane (arrow heads) surrounding the melanocyte with pinocytic vesicles on the cytoplasmic membrane and premature melanosomes. A small melanosome complex is also observed (arrow). Irregularly arranged 80 nm filaments.  $\times 49000$



**Fig. 5.** Clustered SM, which correspond to the naevus cell-like melanocytes observed microscopically.  $\times 4450$



**Fig. 6.** The incidence of FSM of the cervix in total autopsy and surgical specimens. The peak incidence is 17.4% in the fifties, and overall incidence is 8.6%

**Table 1.** Foci of stromal melanocytes (FSM) of the uterine cervix in autopsy and surgical specimens

Age	Autopsy specimens (years)		Surgical specimens	
	No. of cases	No. of cases with FSM (%)	No. of cases	No. of cases with FSM (%)
0-30	28	0 (0)	3	2 (0)
31-40	11	2 (18)	57	2 (3.5)
41-50	32	0 (0)	171	17 (9.9)
51-60	42	6 (14)	44	9 (20)
61-90	86	6 (7)	12	0 (0)
Total	199	14 (7.0)	287	28 (9.8)

to four foci, respectively. The largest noted lesion (shown in Fig. 1a, b) was 12 × 5 mm in size and showed more than ten FSM. The smallest solitary lesion consisted of a single focus with several SM. It was sometimes difficult to count the number of FSM, because of their consistently sparse distribution in the stroma. The melanocytes were noted to be mainly spindle-shaped (Fig. 2a); naevus-like (Fig. 2b) or dendritic-shaped SM (Fig. 2c) were noted occasionally.

Immunohistochemical staining revealed that the many peripheral nerve fibres were distributed in stroma of the cervix, but were seen sparsely in the endometrium or myometrium. The cytoplasm of SM was positive for S-100 protein (Fig. 3a, b). Sometimes peripheral nerve fibres were seen running near the SM, and occasionally enclosing them (Fig. 3b). Electronmicroscopy revealed that the SM has many melanosomes (Figs. 4a, b, 5). Premature melanosomes were found more frequently than mature ones (Fig. 5). Active pinocytotic vesicles, melanin phagocytizing lysosomes and intracytoplasmic intermediate fibres (80 nm) were observed in the melanocytes. The SM were surrounded by a basement membrane (Fig. 5).

The overall incidence of FSM was 8.6% (42/486 cases) (Fig. 6). These lesions were found initially in the

third decade of life and became most prevalent in the fifth decade (15/86 cases, 17.4%). The incidence of FSM in autopsy (7.0%) and/or surgical specimens (9.8%) is shown in Table 1. There was no statistical difference between them.

## Discussion

Cutaneous blue naevus is a blue-coloured solid nodular lesion in the dermis, whereas FSM of the cervix are non-palpable and invisible in most cases. They are not nodular lesions. Even in those cases where the lesions have been observed grossly as brown spots, they were noted to be scattered, irregularly shaped pigmented spots distributed around the cervical glands, without nodular formation or exophytic growth. These findings suggest that FSM are analogous to dermal melanocytosis such as Mongolian blue spot or the naevus of Ota rather than to cutaneous blue naevus. We believe that FSM should be called stromal melanocytosis of the uterine cervix.

We do not refute the existence of a true blue naevus of the cervix. Dorsey and Montgomery (1954) proposed that blue naevus, Mongolian spot and naevus of Ota were closely related and possibly represent different stages of the same process. We speculate that a true blue naevus of the cervix might be an extremely rare manifestation, which might occur secondarily to the less rare FSM of the cervix.

Ultramicroscopically, the dermal melanocytes of Mongolian spot or naevus of Ota have many mature melanosomes in their cytoplasm (Inoue et al. 1973). Our study revealed that the SM in the cervix contained many immature melanosomes. SM also possessed many melanosome complexes suggesting autophagocytic activity of lysosomes. After the fifth decade, the incidence of FSM decreased, which might be associated with autophagosomal activity of the lysosomes in SM.

In the cervical stroma SM were present where many peripheral nerve fibres run but were never observed in the uterine corpus, where nerve fibres were sparsely distributed. SM were positive for S-100 protein and these cells were sometimes close to the nerve fibre branches. It has been reported that certain cells among peripheral nerve cells, unmyelinated nerve ending cells and nerve sheath cells in the dermis of humans and mice have a surprising capacity for melanin synthesis (Garcia and Szabro 1979; Kanno and Kasuga 1987). It is possible that SM of the cervix may be derived from the Schwann cells or perineural cells of nerve tissue.

FSM of the cervix are regarded as acquired lesions because they occur in middle-aged women. Dermal melanocytosis of the face, known as acquired and bilateral naevus of Ota-like macules, is not infrequently observed in middle-aged menopausal Japanese women (Hori et al. 1984) and since FSM and this naevus develop in the same age bracket and in the subepithelial stroma, it is possible that hormonal imbalance in the climacteric might play an important role in the activation of melanogenesis or melanocytic differentiation of the nerve cell.

Cid (1960) detected FSM of the cervix in 6 of 229 cases (2.6%) in Argentina. We found this lesion in 42 of 486 cases (8.6%) in sagittal cross-sectional specimens of the uterus stained with Fontana-Masson stain. Unfortunately, it is impossible to compare our data with those of Cid, because he did not describe his methods in detail and the numbers of specimens he examined from one case is unknown. If we had sliced the entire cervix and examined it consecutively, we might have found this lesion much more frequently. Although FSM of the cervix has been considered rare, our study indicated that this lesion of the cervix is not uncommon, at least in Japanese women.

In Japan, the incidence of mucosal malignant melanoma among melanomas is substantially higher than in the West (21.7–32.0% versus 2%) (Mori 1971; Kasuga 1982). The incidence of the cervico-vaginal melanoma, the aetiology of which is unknown, is higher in Japan than in Western countries (Kasuga 1982). Malignant melanoma of the uterine cervix is a very rare tumour, with only about 20 cases having been described in the literature (Stegner 1959; Abell 1961; Jones et al. 1971; Morrow and Disala 1976; Hall et al. 1980; Mudge et al. 1981; Mordel et al. 1989).

SM in the nasal mucosa (Uehara et al. 1987) and prostate (Nigogosyan et al. 1963) have been suspected to be precursors of mucosal malignant melanoma. SM of the cervix may be precursor cells for cervical melanoma as melanocytes have not been observed in the ectocervical and endocervical epithelium, but only in the stroma. There have been a few case reports of lentigo simplex of the uterine cervix (Schneider et al. 1981; Barter et al. 1988) indicating the presence of melanocytes in stratified squamous epithelium of the ectocervix. These intraepithelial melanocytes may well be the precursor cells of cervical melanoma, but in our studies, we did not find cases with intraepithelial melanocytes in either the ectocervix or endocervix.

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