Giant Congenital Nevus and Malignant Melanoma

Yoshiaki Hori, M.D., Juichiro Nakayama, M.D., Mitsuse Okamoto, M.D., Shonosuke Nagae, M.D., Shunichiro Taniguchi, M.D., Osami Takayama, M.D., and Kuniaki Oohara, M.D.

Department of Dermatology, Kyushu University, Faculty of Medicine, Fukuoka (YH, JN, MO, SN); Medical Institute of Bioregulation, Kyushu University, Fukuoka (ST); Department of Dermatology, Yamanashi Medical College, Yamanashi (OT); and Department of Dermatology, Toranomon Hospital, Tokyo, Japan (KO)

Frequency of malignant transformation arising in giant congenital nevi is considered to be 4% – 5%. More than a half of the patients in which malignant melanoma developed in giant congenital nevi were under the age of 10. It may be hypothesized that dermabrasion of giant congenital nevus may provoke malignant transformation.

Some of the cell groups in giant congenital nevus are potentially malignant. Some groups of nevus cells were larger in size than those of other portions of nevus. Electron microscopic observation revealed that nuclei of these larger nevus cells were significantly indented, and melanization of melanosomes was irregular.

Coexistence of α-like actin with β- and γ-actins in giant congenital nevus cells and disappearance of α-like actin in malignant melanoma cells were noted. *J Invest Dermatol 92:310S – 314S, 1989*

Malignant melanoma may arise de novo, as well as in association with preexisting pigmented lesions. These preexisting lesions include dysplastic nevi, common acquired nevi, and congenital nevi [1].

Although the association between malignant melanoma and giant congenital nevi is well known, a proper explanation for the malignant transformation from giant congenital nevus has not been made. Possible related factors include a larger number of pigmented cells, certain potentially malignant nevus cells [2], and a deficiency of oxygen or an increase of CO_2 in tissues.

This paper deals with statistical studies of malignant transformation of giant congenital nevi, a case of malignant change in a giant congenital nevus, abnormal morphologic features of giant congenital nevus cells, and biologic differences between giant congenital nevus cells and malignant melanoma cells.

Definition of Giant Nevus The definition of giant nevus varies from author to author. For example, Pers [3] defines a giant nevus as palm-sized on the face and twice palm size elsewhere; Greeley defines it as a lesion that covers an area greater than 144 square inches [4]; Kaplan defines it as a lesion that "cannot be excised without significant deformity" [2]; and Kopf et al suggest an arbitrary size of 20 cm or larger [5]. For the dermatomal distributions of nevi, "bathing trunk," "vest-like," "vest with collar," "garment," "cape-like," "coat-sleeve," "stocking-like," and so on are designated for giant congenital nevi (GCN) by several authors [6].

Clinical features of GCN include 1) grossly irregular surface, 2) increased pigmentation with varying shades of brown, and 3) hypertrichosis [1].

Incidence of Malignant Transformation in Giant Congenital Nevi The frequency of giant congenital nevi progressing into malignant melanoma (MM) has been estimated from 2% to 42% in the US and Europe [2,7]. In Japan, three different groups estimated the incidence of malignant melanoma arising in giant congenital nevi to be 3.2% to 5.6% (Table I) [8].

Age distribution of the incidence of malignant melanoma in giant congenital nevi is shown in Table II [2]. More than half of the patients in which malignant melanoma developed were under age ten.

Lorentzen et al [9] estimated the lifetime risk of malignant degeneration to be 4.6% in patients with giant congenital nevi, assuming that the incidence was the same in all age groups from the data and life expectancy in Denmark (72.8 years of age in 1980).

Rhodes et al [10], however, estimated the lifetime risk to be at least 6.3% because the risk is probably higher among the young, as described above, yielding an approximately 17-fold risk for malignant melanoma, compared with the general population.

Surgical removal of giant congenital nevi could have lowered the percentage of malignant transformation. On the other hand, nonradical treatment such as cryotherapy, partial excision, or dermabrasion may provide a malignant transformation [11]. Some patients with giant congenital nevi were treated and developed malignant melanoma after dermabrasion of nevi [12]. Oryu et al [12] reported a patient who received dermabrasion of giant congenital nevi twice, developed malignant melanoma 8 months after the second dermabrasion, and died from malignant melanoma 4 months later.

Histologic and ultrastructural studies of nonmalignant nodules in giant congenital nevi revealed that the nuclei of nevus cells were significantly indented, and these nevus cells contained abnormally melanized melanosomes.

Case Report

Case 1: A baby girl had a blue-black macule extending from the occipital region of her head down to the upper back since birth (Fig 1). At the age of 2 months, dermabrasion of the upper back was performed. Three months after the dermabrasion, a subcutaneous nodule was evident in the treated area which was subsequently resected (Fig 2). Histologic observation demonstrated melanoma cells in the subcutaneous tissue (Figs 3 and 4).

Case 2: A baby girl had garment-type giant congential nevi on the neck, back, hip, buttocks, and abdomen. Several soft black nodules were noted on the upper back (Fig 5). These soft nodules were resected, and the histology of these nodules was studied under light

Reprint requests to: Yoshiaki Hori, M.D., Ph.D., Kyushu University, Faculty of Medicine, Fukuoka, Japan.

Abbreviations:
GCN: giant congenital nevi
MM: malignant melanoma

0022-202X/89/$03.50

Table I. Incidence of Malignant Melanoma Arising in Giant Congenital Nevi in Japan

Authors	MM/GCN[a]	%
1. Osmui T, Seiji M, 1983 [8]	4/87	4.6
2. Ikeda S, Muzutani H, 1981[b]	2/36	5.6
3. Oohara K, 1987[b]	1/31	3.2
TOTAL	7/154	4.5

[a] MM: malignant melanoma; GCN: giant congenital nevi.
[b] Personal communications.

Table II. Incidence of Malignant Melanoma in Giant Congenital Nevi: Age Distribution

Kaplan et al, 1974 [2]		Dermatosurgery Study Group in Japan, 1987[a]	
Age (year)	Number	Age (year)	Number
At birth	8		
0–5	15	0–4	6
6–10	6	5–9	2
11–15	4	10–24	0
16–20	2	25–29	1
21–30	4	30–	3
31–	14		
Total		Total	
Number of Patients	53	Number of Patients	12
% ≤ 10	54.7%	% ≤ 10	66.7%

[a] Personal communication.

and electron microscopes. Some groups of cells were larger in size than those of other portions of nevus (Figs 6 and 7). Electron microscopic observation revealed that nuclei of these larger nevus cells were significantly indented (Fig 8), and melanization of melanosomes was irregular (Fig 9).

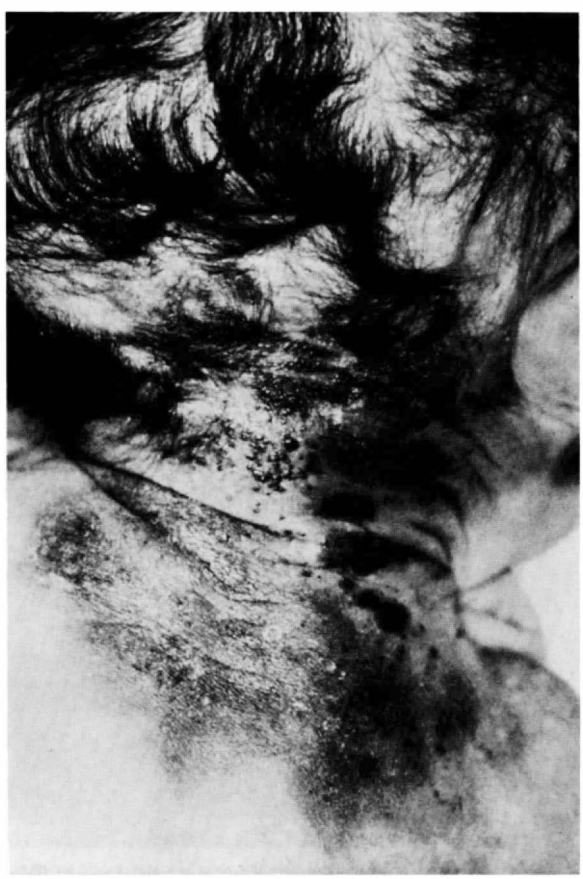

Figure 1. Clinical features of Case 1 at the age of 1 month.

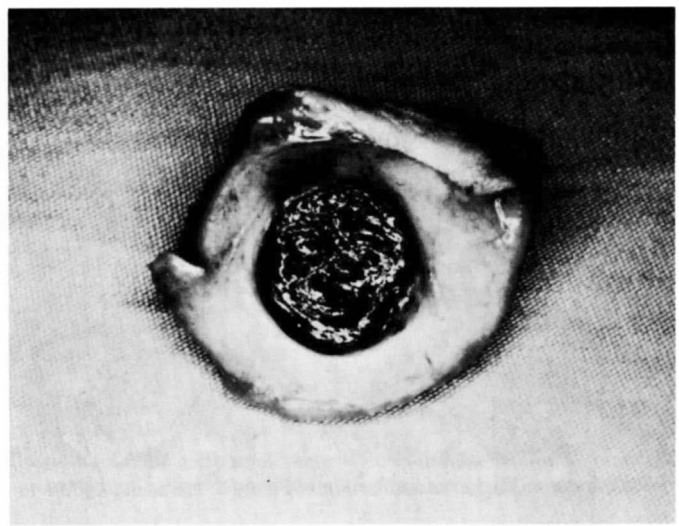

Figure 2. Subcutaneous black nodule of case 1, 4 months after dermabrasion of nevus.

Biological Differences Between Giant Congential Nevi and Malignant Melanoma Cells Actin is a major component of cytoskeletal proteins, and its alteration has been associated with malignant transformation. So far, six isomers of actin have been identified in normal vertebrate cells [13,14]. By isoelectric focusing, these isomers can be classified into three species [α, β, and γ). The α-actins are the most acidic of the three species, and tissue-specific α-type isomers are found in skeletal and cardiac muscle and vascular smooth muscle cells. Ordinary non-muscle cells express only β and γ actins, and another γ-like actin is present in smooth muscle cells from chicken gizzard. In addition to these normal actins, point-mutated β-actin [15–17] has been detected in a transformed human fibroblast cell line, the expression of which correlates with tumorigenicity of the cells [18]. Another transformation-sensitive α-like actin was demonstrated in cultured chick embryo fibroblast [19], mouse NIH 3T3 cell line, and Rat-2 cells [20]. In B16 mouse melanoma cells, Taniguchi et al [21] detected a variant actin (A^z) which decreases or disappears concomitantly with an increase in the metastatic ability of the cells. They also reported that α-like actin, in addition to non-muscle β- and γ-actins, was found in human benign pigment tissues but not in malignant melanomas [22].

Tissue from a 4-year-old girl with giant congenital nevi was minced, dissolved in O'Farrell's lysis buffer, and subjected to two-dimensional polyacrylamide gel electrophoresis.

On the gel stained with Coomassie blue, a spot (A′) slightly more

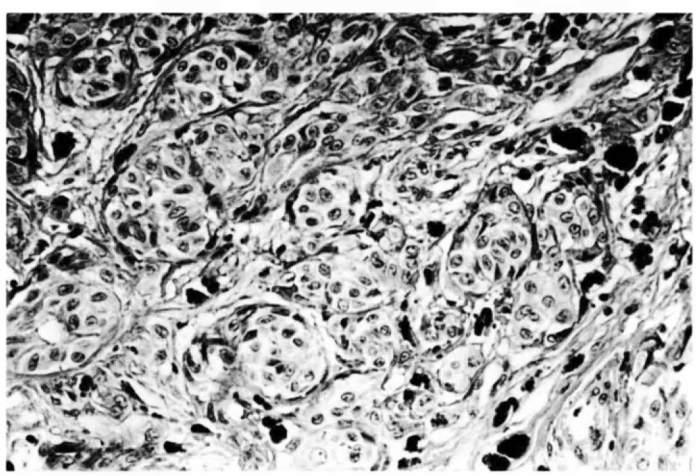

Figure 3. Histology of subcutaneous black nodule of case 1, HE stain (×300).

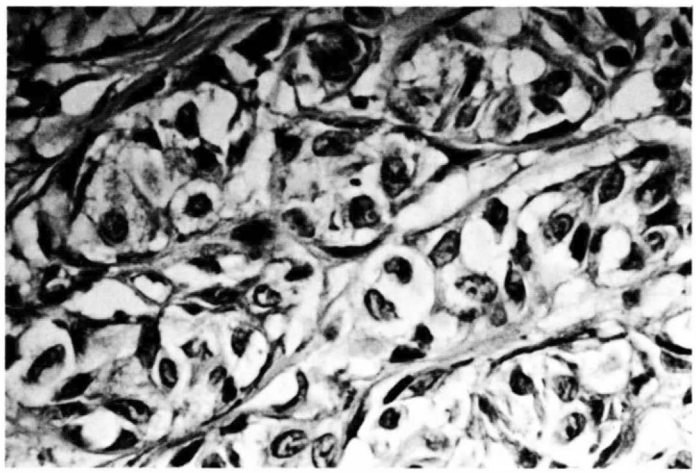

Figure 4. Higher magnification of Figure 3, HE stain (×600).

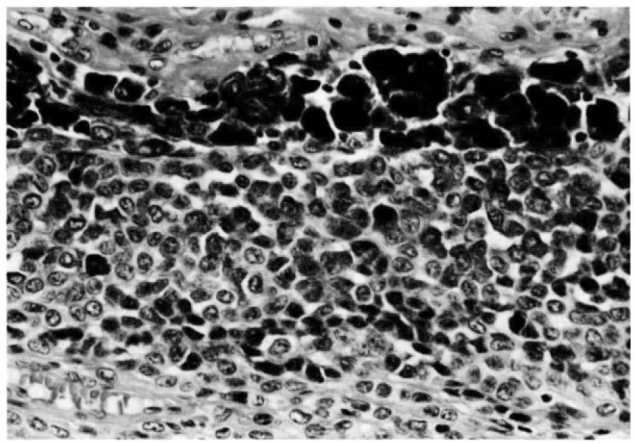

Figure 6. Histology obtained from a soft black tumor of Case 2, HE stain (×200).

acidic than β and γ actins was visualized. When the proteins were further analyzed by Western blot and immunostained, the third α-like spot reacted with anti-actin monoclonal antibody, as did authentic muscle actin, β, and γ actins (Fig 10). This finding indicates that the third spot is an actin isomer.

Tissue from a 39-year-old woman with nodular malignant melanoma and metastasis in the left femoral lymph nodes was analyzed. Two-dimensional electrophoresis and silver staining were performed to examine the proteins extracted from the specimen. No spot adjacent to β and γ actins was detected. Disappearance of α-like actin was confirmed by Western blot analysis (Fig 11).

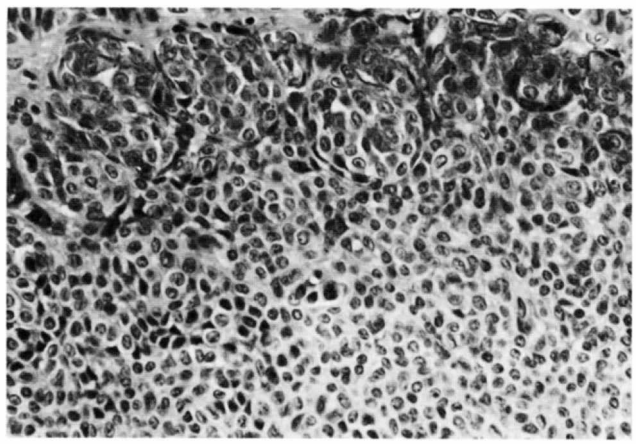

Figure 7. Histology obtained from a flat portion of giant nevus of Case 2, HE stain (×200).

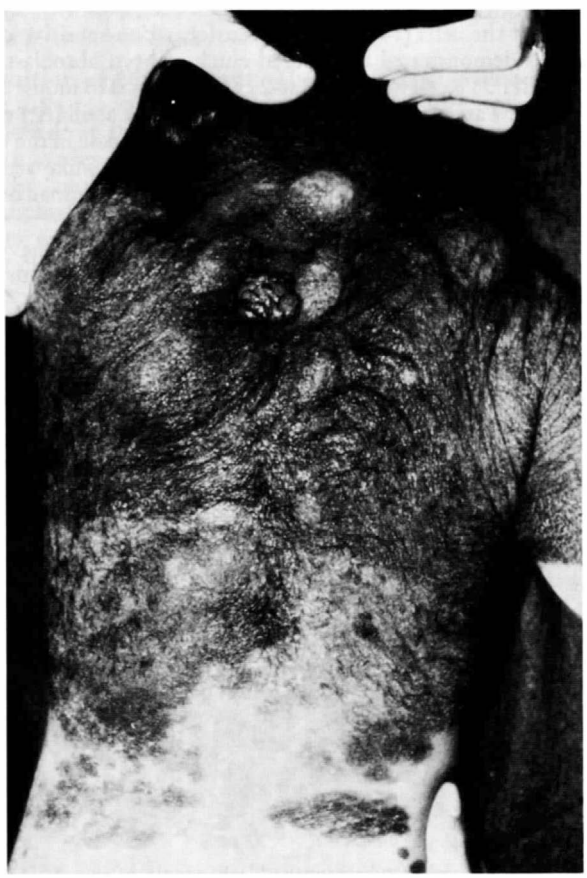

Figure 5. Several soft black tumors of Case 2.

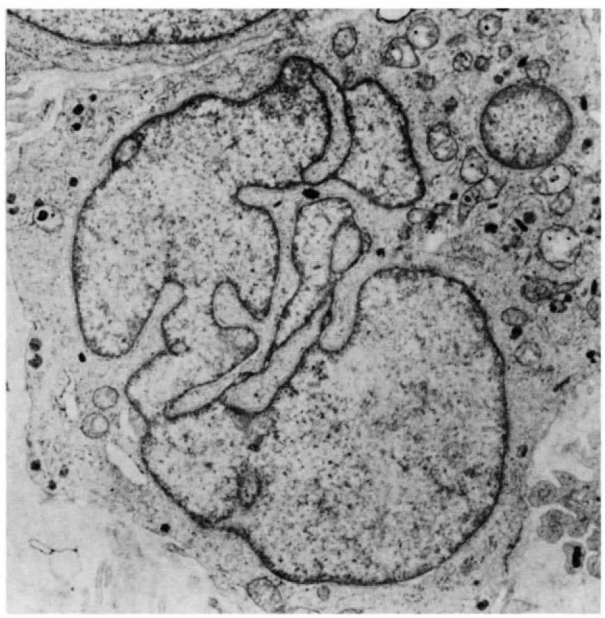

Figure 8. Electron photomicrograph of a nevus cell obtained from a soft black nodule, uranyl acetate, and lead citrate stain (×6000).

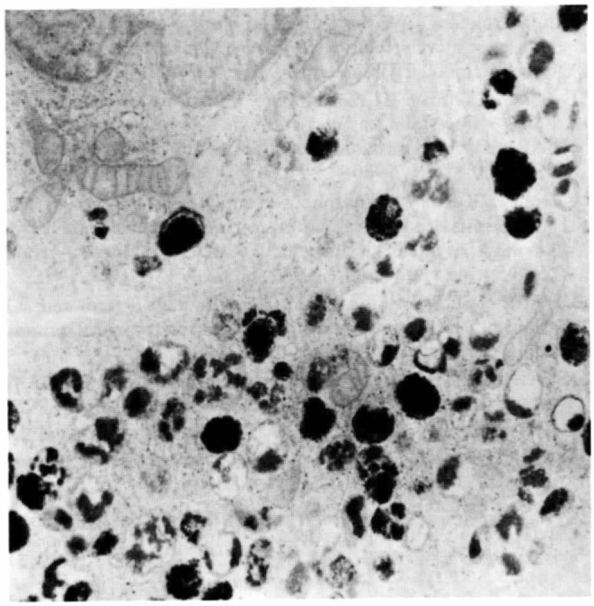

Figure 9. Electron photomicrograph of irregularly melanized melanosomes on nevus cells obtained from a soft black nodule, uranyl acetate, and lead citrate stain (×20,000).

DISCUSSION

The incidence of malignant transformation from giant congenital nevi has varied between 1.8% and 42% [2,3,7]. This difference in frequency by authors may be due to how the total number of giant congenital nevi were collected and also to the varying definition of "giant." It is not easy to count the exact number of giant congenital nevi and also the exact number of the patients with giant congenital nevi who developed malignant melanoma.

Lorentzen et al [9] estimated the lifetime risk of malignant degeneration to be 4.6% in patients with giant congenital nevi, assuming the yearly rate of malignant change to be constant. Rhodes et al [10], however, estimated the lifetime risk to be at least 6.3%, taking into consideration that the risk is probably higher among the young. Although malignant transformation in giant congenital nevi may develop at any age, nearly 60% of these malignant melanomas developed during the first decade of life, as shown in Table II [2].

Three different groups in Japan estimated the incidence of malignant melanoma arising in giant congenital nevi to be 3.2% to 5.6% [8]. Therefore, the frequency of malignant transformation from giant congenital nevi is about 5%, which seems reasonable and is in the same range as estimated for transformation in whites.

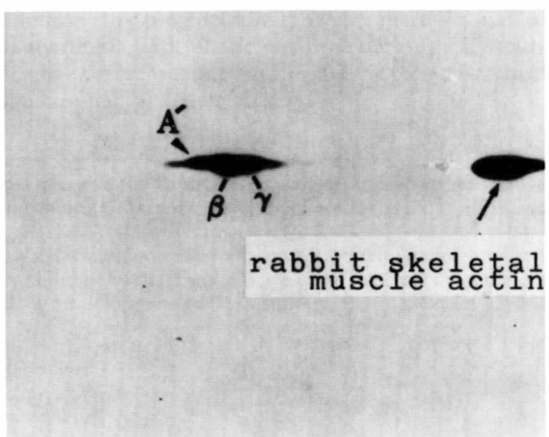

Figure 10. α-like, β and γ actins were detected in tissue from a 4-year-old girl with giant congenital nevus by Western blot analysis and immunostain.

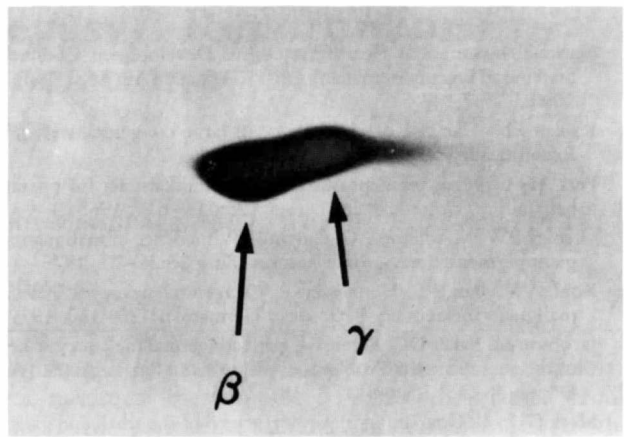

Figure 11. Only β and γ actins were detected in tissue from a 39-year-old woman with nodular malignant melanoma and metastasis in lymph nodes.

Surgical elimination of giant congenital nevi could have lowered the percentage of malignant transformation. On the other hand, it may be hypothesized that non-radical treatment such as cryotherapy, electrotherapy, partial excision, or abrasion may provoke a malignant transformation. One reported case in Japan developed malignant melanoma after two dermabrasions [12].

The complete and extensive resection of giant nevi in order to prevent the development of a malignant neoplasm is not practical because of the size of the nevus and the deep penetration of nevus cells, sometimes even into the underlying muscle [6].

Borges and Lineberger [23] suggest that malignant melanoma arising from giant congenital nevi might sometimes be relatively nonaggressive. In fact, in our case, one is still free of recurrent melanoma months after removal of the primary tumor.

There is considerable controversy concerning the surgical treatment of giant congenital nevi. The management of giant congenital nevi depends primarily on the size and the perceived risk or development of malignancy. These lesions should be periodically documented, measured, and observed for alterations of their size, color, and topography [1].

A proper explanation for the malignant transformation from giant congenital nevi has not been established. Kaplan [2] postulated that 1) there could be a much greater number of melanocytes, and 2) there might be an increased malignant potential of certain histologic types of nevus cells in giant congenital nevi [2]. We hypothesized the possibility of a deficiency of oxygen or an increase of CO_2 in tissues of giant congenital nevi.

Disappearance of α-like actin in tissues of malignant melanoma may be evidence that alteration of cytoskeletal proteins is one of the important processes in malignant transformation and/or progression, although functions and characterizations of the α-like actin which disappears in cells of malignant melanoma have yet to be investigated. Furthermore, these results suggest that analysis of actin may serve as an aid for diagnosis of benign and malignant pigment tissues.

SUMMARY

Frequency of malignant transformation arising in giant congenital nevi is about 5%. It may be hypothesized that dermabrasion of giant congenital nevus may provoke malignant transformation. Some of the cell groups in giant congenital nevus are potentially malignant.

Co-existence of α-like actin with β and γ actins in giant congenital nevus cells and disappearance of α-like actin in malignant melanoma cells were noted in our study.

The authors are very grateful to Dr. K. Ishihara, Dr. Y. Tanaka, Dr. K. Kumano, Dr. R. Shimizu, and Dr. T. Miyazaki from the Department of Dermatology, Hyogo Medical College and Dermatosurgery Study Group, Japan, for providing their data.

REFERENCES

1. National Institutes of Health Consensus Development Conference Statement: Precursors to malignant melanoma. J Am Acad Dermatol 10:683–687, 1984
2. Kaplan EN: The risk of malignancy in large congenital nevi. Plast Reconstr Surg 53:421–428, 1974
3. Pers AFM: Nevus pigmentosus gianticus: Indikationer for operative behandling. Ungeskrift for Laeger 125:613–619, 1963
4. Greeley PW, Middleton AG, Curtin JW: Incidence of malignancy in giant pigmented nevi. Plast Reconstr Surg 36:26–37, 1975
5. Kopf AW, Bart RS, Hennessey P: Congenital nevocytic nevi and malignant melanomas. J Am Acad Dermatol 1:123–130, 1979
6. Jacobson M, Baker DC: Extensive giant congenital melanocytic nevus of the face and scalp. Problems of diagnosis and management. Am J Dermatopathol 7(suppl):177–181, 1985
7. Mark GJ et al: Congenital melanocytic nevi of the small and garmnet type. Human Pathol 4:395–418, 1973
8. Osumi T, Seiji M: Statistical observations of malignant melanoma in Japan. Hifuka-No-Rinsho 15:6–31, 1973 (in Japanese)
9. Lorentzen M, Pers M, Bretteville-Jensen G: The incidence of malignant transformation in giant pigmented nevi. Scand J Plast Reconstr Surg 11:163–167, 1977
10. Rhodes AR et al: Nonepidermal origin of malignant melanoma associated with a giant congenital nevocellular nevus. Plast Reconstr Surgery 67:782–790, 1981
11. Shaw MH: Malignant melanoma arising from giant hairy nevus. Br J Plast Surg 15:426–435, 1962
12. Oryu F et al: Infantile malignant melanoma arising in giant pigmented nevus. Hifuka-No-Rinsho 29:747–750, 1987 (in Japanese)
13. Vandekerchkove J, Weber K: At least six different actins are expressed in a higher mammal: An analysis based on the amino acid sequence of the amino-terminal tryptic peptide. J Mol Biol 126:783–802, 1978
14. Vandekerchkove J, Weber K: Actin typing on total cellular extracts: A highly sensitive protein-chemical procedure able to distinguish different actins. Eur J Biochem 113:595–603, 1981
15. Leavitt J, Kakunaga T: Expression of variant forms of actin and additional polypeptide changes following chemical-induced in vitro neoplastic transformation of human fibroblasts. J Biol Chem 255:1650–1661, 1980
16. Kakunaga T et al: A point mutation and other changes in cytoplasmic actins associated with the expression of transformed phenotypes. In: Levine AJ et al (eds.). Cancer Cells. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1984, pp 67–74
17. Leavitt J et al: Expression of transfected mutant β-actin genes: Alterations of cell morphology and evidence for autoregulation in actin pools. Mol Cell Biol 7:2456–2466, 1987
18. Leavitt J et al: Expression of transfected mutant β-actin genes: Transitions toward the stable tumorigenic state. Mol Cell Biol 7:2467–2476, 1987
19. Witt DP, Brown DJ, Gordon JA: Transformation-sensitive isoactin in passaged chick embryo fibroblasts transformed by Rous sarcoma virus. J Cell Biol 96:1766–1771, 1983
20. Leavitt J et al: Smooth muscle α-actin is a transformation-sensitive marker for mouse NIH-3T3 and Rat-2 cells. Nature 316:840–842, 1985
21. Taniguchi S et al: Differences in expression of a variant actin between low and high metastatic B16 melanoma. J Biol Chem 261:6100–6106, 1986
22. Taniguchi S, Nakayama J, Urabe H: Difference of actin-like protein between human benign and malignant tissues. Proc Jpn Soc Invest Dermatol 1:38–39, 1987
23. Borges AF, Lineberger AS: Malignant melanoma without metastasis in a giant nevus. Ann Plast Surg 12:454–460, 1984