

Bull Yamaguchi Med Sch 42(1-2) : 45-47, 1995

## A Case with Neutrophil Infiltration into Nevus Cell Nest after Intravenous Administration of Interferon- $\beta$

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(Received June 1, 1994, Revised June 15, 1995)

**Abstract** Interferon- $\beta$  therapy has been widely applied for patients with hepatitis C and with malignant melanoma. Its anti-tumor effects on malignant melanoma are well discussed but few reports on anti-tumor effect of the interferon- $\beta$  to benign tumors are described. A 63-year-old female received interferon- $\beta$  therapy (dose =  $6 \times 10^6$  units/day) for hepatitis C and developed erythematous change and pain on her intradermal nevus seen on the right external canthus. Histopathological study revealed that the neutrophilic infiltration was localized only in nevus cell nest. It seems interferon- $\beta$  worked on nevus cells and led the nevocytes to secrete cytokines such as IL-8. A possibility that there is one pathway on anti-tumor effects related to melanin-producing cells, via the neutrophils, is suggested.

*Key Words* : intradermal nevus, interferon, neutrophil, anti-tumor effect

### INTRODUCTION

A cytokine of interferon- $\beta$  has been clinically used because of several biological activities involving anti-tumor effects. The therapy using interferons has gained a great interest in the dermatological field, and intralesional administration of interferon- $\beta$  has proved to be effective in treatment of malignant melanoma. Many investigators have reported on its anti-tumor effects, but few on its anti-benign tumor effects. We present an interesting case of a patient who had received interferon- $\beta$  therapy for hepatitis C, developed erythematous change on nevus cell nevus.

### CASE PRESENTATION

A 63-year-old female with redness and tenderness on the right external canthus visited our Dermatological Clinic in May 1992. In May 1991, she felt general fatigue and had fever up to 38°C. Liver dysfunction was suspected and in July 1991, the diagnosis of chronic hepatitis (CAH-2A due to HCV) was made at the First Department of Internal Medicine of our University. In April 1992, interferon- $\beta$  treatment started and six million units per day of interferon- $\beta$  were intravenously administered. Three days after the initiation of interferon- $\beta$  treatment, she found redness and tenderness on the right external canthus and consulted us. Family history and past histories were not remark-

able. Laboratory data were transaminases GOT 67u; GPT 31u; ALP 11.9u; HCV-Ab(+); HCV-Ab IOD 1.087(cut-off 0.204); RBC  $395 \times 10^4/\text{mm}^3$ ; Hb 11.9g/dl; Plt  $10.4 \times 10^4/\text{mm}^3$ ; WBC  $4000/\text{mm}^3$  total protein 7.3g/dl; albumin 3.4g/dl. Laparoscopy showed dark reddish liver with irregular surface. Von Mayenberg's complex was positive. Ultrasonography of the gall bladder showed whitish thickened wall that suggest chronic cholecystitis.

A bean-sized reddish-brownish colored hemisphere papule with red halo was present in the right external canthus when she first visited us. Its smooth surface had no pus nor erosive change(Fig. 1). Biopsy specimens were obtained from the papule after complete resection (Fig. 2). Histopathologically, the nevus cells composed of fairly well circumscribed nests in the dermis. Neither junctional activity nor cleft formation was seen. The nevus cells had epithelioid shape. Histopathological diagnosis was intradermal epithelioid type of nevus cell nevus. Additionally, the dermis appeared to be edematous with a moderate degree of vasodilation. The edema caused a loose arrangement of the nevus cell nests. The margin of the nevus cell nest was clearly bordered and inflammatory infiltration was not seen outside the nevus cell nest(Fig. 3). In the center of the nest, the infiltration of neutrophils was predominantly observed(Fig. 4). The high power field of the



Figure 1. A clinical feature at the first visiting our Clinic. On the right external canthus, a bean-sized, reddish-brownish colored hemisphere papule with red halo appeared.

nest revealed some neutrophils firmly attached to nevus cells without showing any nevus cell lysis(Fig. 5).

Skin tests using interferon- $\beta$  were negative at both 15 minutes and 48 hours after administration, showing neither immediate nor delayed types of hypersensitivity by it.

## DISCUSSION

Intradermal nevus often grows in size after middle-aged individuals. The mecha-



Figure 2. A low power field of nevus cell nest( $\times 4$ ). A bean-sized, hemisphere papule was total resected. Specimens obtained after resection, and then H-E staining was done.

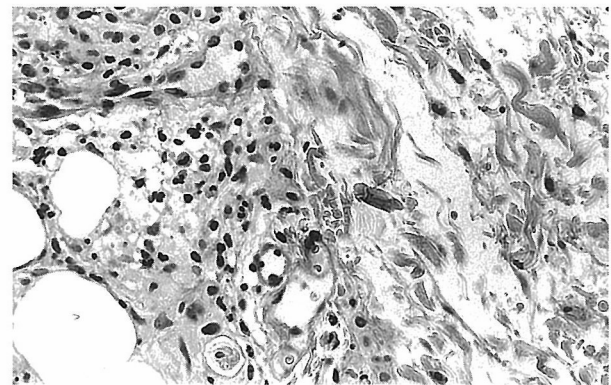


Figure 3. The margin of the nevus cell nest( $\times 100$ ). Within the nest, there're nevus cells and neutrophilic infiltration, although there're no extralesional neutrophilic infiltrations.

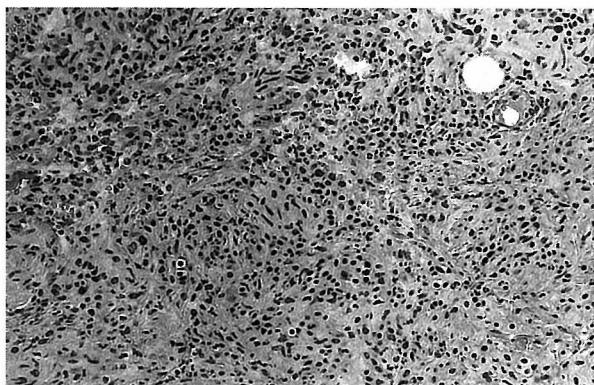


Figure 4. Middle power field of the center of the nest ( $\times 40$ ). Marked neutrophilic infiltration is seen.

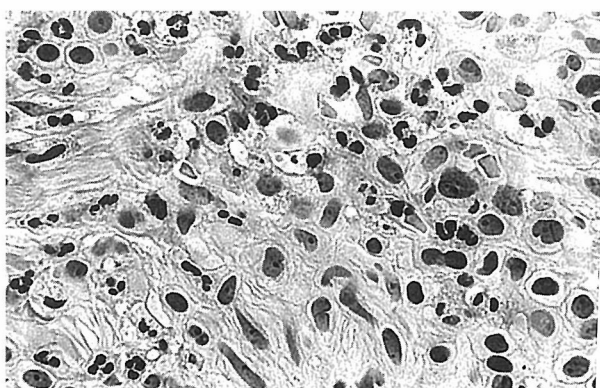


Figure 5. High power field of figure 4 ( $\times 400$ ). Some neutrophils attach to nevus cells are seen.

nisms of enlargement of the are considered as follows: first, numerical proliferation of nevus cells. Second, enlarged each nevus cell. Third, interstitial proliferation of matrix. Fourth, inflammatory cell infiltration. Fifth, cleft formation. The possibilities of 1, 2 and 3 are considered to be the mechanism of nevus growth with aging. The 5 is called as Spitz nevus<sup>(1)</sup>. In our case, marked inflammatory cells of infiltration was seen. But there were no signs of local infection. Spitz nevus is ruled out because of no cleft formation. Until now, biological functions of the nevocytes have not been clear. We can speculate that interferon- $\beta$  worked on nevus cells and led

the nevocytes to secrete cytokines such as IL-8(interleukin 8) with neutrophil-attractant activity.

In the dermatological field, interferons first came into use in 1970's as a local injection therapy for melanoma<sup>(2)(3)</sup>. Then interferon- $\beta$  therapies for condyloma accuminatum and verruca juvenilis showed an effect diminishing the tumors<sup>(4)</sup>. Regarding anti-tumor effects of interferon- $\beta$ , inductions of cytotoxic T cells and/or natural killer cells have been reported<sup>(5)(6)(7)(8)</sup>. In contrast, neutrophils showing cognate interaction with the nevocytes were observed in the present case, whereas lymphocytes were not infiltrated in the nevus nest. Both nevus cells and melanocytes, in which melanoma cells develop, are of neural crest origin.

At the same time, therapy using interferons is now the first choice for treatment of hepatitis C<sup>(9)</sup>, and our patient with intradermal nevus had been under intravenous injection of interferon- $\beta$  for three days.

Further study is necessary to consider interferons in a new aspect of its antitumor effect.

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