INTRALESIONAL INTERFERON ALFA-2a THERAPY IN ADULT HEMANGIOMAS

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N. Durak, M.D. / E. Kışlaoğlu, M.D.* / F. Yüksel, M.D.******
İ. Okar, M.D. * / T. Şan, Ph.D.*******

* *Professor, Department of Plastic and Reconstructive Surgery, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.*
** *Associate Professor, Department of Plastic and Reconstructive Surgery, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey.*
*** *Associate Professor, Department of Histology, Faculty of Medicine, Marmara University, Istanbul, Turkey.*
**** *Resident, Department of Plastic and Reconstructive Surgery, Gülhane Military Medical Academy, Haydarpaşa Training Hospital, İstanbul, Turkey*
***** *Resident, Department of Histology, Faculty of Medicine, Marmara University, Istanbul, Turkey.*

SUMMARY

Hemangiomas, mostly appearing in infancy, generally involute completely and with their complications, rarely demand medical or surgical intervention. On the other hand, hemangiomas of adult life are persistant and usually no problems other than cosmetic ones accompany the lesions. So, appropriate methods, with no complications and side effects, must be preferred in the treatment. Most of the prior methods are usually inadequate in the management of the process.

Regression effect of systemic interferon treatment on infantile hemangiomas was perceived before. Similarly, we injected interferon alfa-2a into the adult hemangiomas three times a week, for three weeks and observed regression of the lesions by morphologic, histopathologic and ultrastructural evaluation.

Key Words: Hemangiomas, interferon alfa-2a, adult life.

INTRODUCTION

Hemangioma is the most common tumor of infancy, occurring in 10-12 % of population, and in up to 22 % of preterm babies weighing less than 1000 g.(1,2). It is characterized by the proliferation of capillary endothelium with multilamination of the basement membrane and the accumulation of mast cells, fibroblasts and macrophages (3).

Histologically, hemangiomas may form capillary or cavernous structures. Capillary hemangiomas account for 75 % of them and are composed of masses of endothelial cells exhibiting modest amount of differentiation, frequently without discrete capillary formation (4). Cavernous hemangiomas are less common and commonly deeper in the dermis with larger vascular channels and less distinct clinical margins. The rarity with which these lesions exhibit regression suggests that they are composed of vessels lined with mature endothelial cells. They usually persist as residual deformities (5).

Many interventive or non-interventive methods of hemangioma treatment such as selective ligation, compression, injection of sclerosants, cryotherapy, radiotherapy and embolization have been utilized in the past but none of them were acceptable enough and associated with various undesirable side effects (6-8). Systemic or local steroid control of hemangiomas usually gives better results than any other methods and some authors declared palliation in life threatening lesions (9,10). At present, various types of lasers offer great promise for a wide variety of hemangioma treatment. The most effective and applicable ones for use in these lesions include the argon, carbon dioxide, YAG and tunable dye lasers (11,12), but , there are still arguments about their results. Even not applicable in every case, one must consider partial or complete surgical excision as the last choice for management.

More troublesome hemangiomas maintain their presence in the adult lives because most surgeons hesitate to do something to the ones on critical locations before. So, they must be treated or gotten into considerable dimensions with confidence. That is why the treatment modality causing the least morbidity and the best results should be selected for the treatment of adult hemangiomas.

MATERIAL AND METHOD

The study involved 14 hemangiomatous lesions of 12 patients (4 female/8 male). Their ages ranged from 18 to 42. Baseline hematologic, hepatic, and renal function studies were performed and written informed consent was obtained from all patients. Criteria for

exclusion from this study included serious intercurrent illness, patients with a family history of autoimmune disease, patients with a central nervous system disorder, pregnant or lactating women and anyone who had received prior interferon therapy.

Eight lesions in the treatment group were treated by intralesional recombinant interferon alfa-2a injection three times a week, for three weeks.In each injection, 9 million u .active material (1 ml.) was given uniformly into the lesion with a 27 gauge needle. Six lesions in the control group were treated by 1 ml. saline injection as placebo at the same intervals as the other group.

The widest external diameters and the heights of the lesions were measured and photographed at the beginning and end of the treatment and one month after the last injection. In the treatment group, the external diameters of lesions were 20,24,35,18,16,32,12 and 14 mm. and the heights were 5,8,4,6,4,10,8 and 6 mm. : whereas in the control group, the external diameters were 18,24,20,36,18,26 mm. and the heights were 6,10,6,4,6 and 5 mm. respectively.

At the beginning and one month after the treatment, tissue specimens from the treatment group were harvested for histo-pathological and electronmicroscopic evaluation.

RESULTS

When the hemangiomas were evaluated at the end of one month after the treatment, more than 20 % regression in the external diameters and heights of 7 lesions in the treatment group was observed while none of the lesions in the control group showed any considerable regression (Tables I, II; Figs. 1,2). At that time, the values of external diameters and regression rates in the treatment group were 14 (30%),12 (50%), 28 (20%), 14 (22%), 10 (37%), 28 (13%), 8 (33%) and 9 mm.(36%) ; and for the heights, they were 3 (40%), 6 (25%), 3 (25%), 4 (33%), 2 (50%), 9 (10%), 6 (25%) and 4 mm.(33%) successively.

In the control group, the external diameters and regression rates were l8 (0%), 22(8%), 20 (0%), 34 (6%), 18 (0%), 24 mm.(8%) and the heights and regression rates were 8 (0%), 9 (10%), 6 (0%), 4 (0%), 6 (0%) and 5 mm.(0%) successively.

As the adverse effects, one patient in the control group experienced skin rash at the injection site. Of the treatment group, 6 patients had fever that responded to acetaminofen 500 mg., 3 patients experienced mild nausea and 2 patients had headache and myalgia. These symptoms and signs were not observed again after the third injections.

On histopathological examination of the treatment group, endothelial cell masses creating lots of wide cavernous structures were observed in the specimens harvested at the beginning of the treatment. In the specimens taken one month later, widespread fibrosis and hyalinization were noticed. (Fig. 3). Cavernous structures on every microscopic view from each group were counted and compared. The number was halved at the end of the treatment. In addition, micrometric measurement of the lumens showed about 50 % decrease in diameter. Examination with JEOL 1200 EX 11 Transmission electronmicroscope revealed reduced capillary luminal spaces and endothelial cells projected into the lumens that can mean vasoconstriction. Widespread collagen fibrils accompanied by fibroblasts and macrophages were established all around the parivascular areas due to fibrosis (Fig.4).

Statistical assessment with student-T test revealed that the difference between the treatment and the control groups for ensuring regression more than 20 % was significant in favor of the former one (Mean value for Group 1: 30.1; for Group 2: 3.6; T 5.3, $p<0.05$).

Table I- Values of external diameters, heights and the regression rates of lesions in the treatment group before and one month after the treatment.

	TREATMENT GROUP					
	BEFORE TREATMENT		AFTER TREATMENT			
No.	Ext. Dia. (mm.)	Height (mm.)	Ext. dia. (mm.)	Regr. Rate (%)	Height (mm.)	Regr. Rate (%)
1	20	5	14	30	3	40
2	24	8	12	50	6	25
3	35	4	28	20	3	25
4	18	6	14	22	4	33
5	16	4	10	37	2	50
6	32	10	28	13	9	10
7	12	8	8	33	6	25
8	14	6	9	36	4	33

Table II- Values of external diameters, heights and the regression rates of lesions in the control group before and one month after the treatment.

CONTROL GROUP						
	BEFORE TREATMENT		AFTER TREATMENT			
No.	Ext. Dia. (mm.)	Height (mm.)	Ext. dia. (mm.)	Regr. Rate (%)	Height (mm.)	Regr. Rate (%)
1	18	8	18	0	8	0
2	24	10	22	8	9	10
3	20	6	20	0	6	0
4	36	4	34	6	4	0
5	18	6	18	0	6	0
6	26	5	24	8	5	0

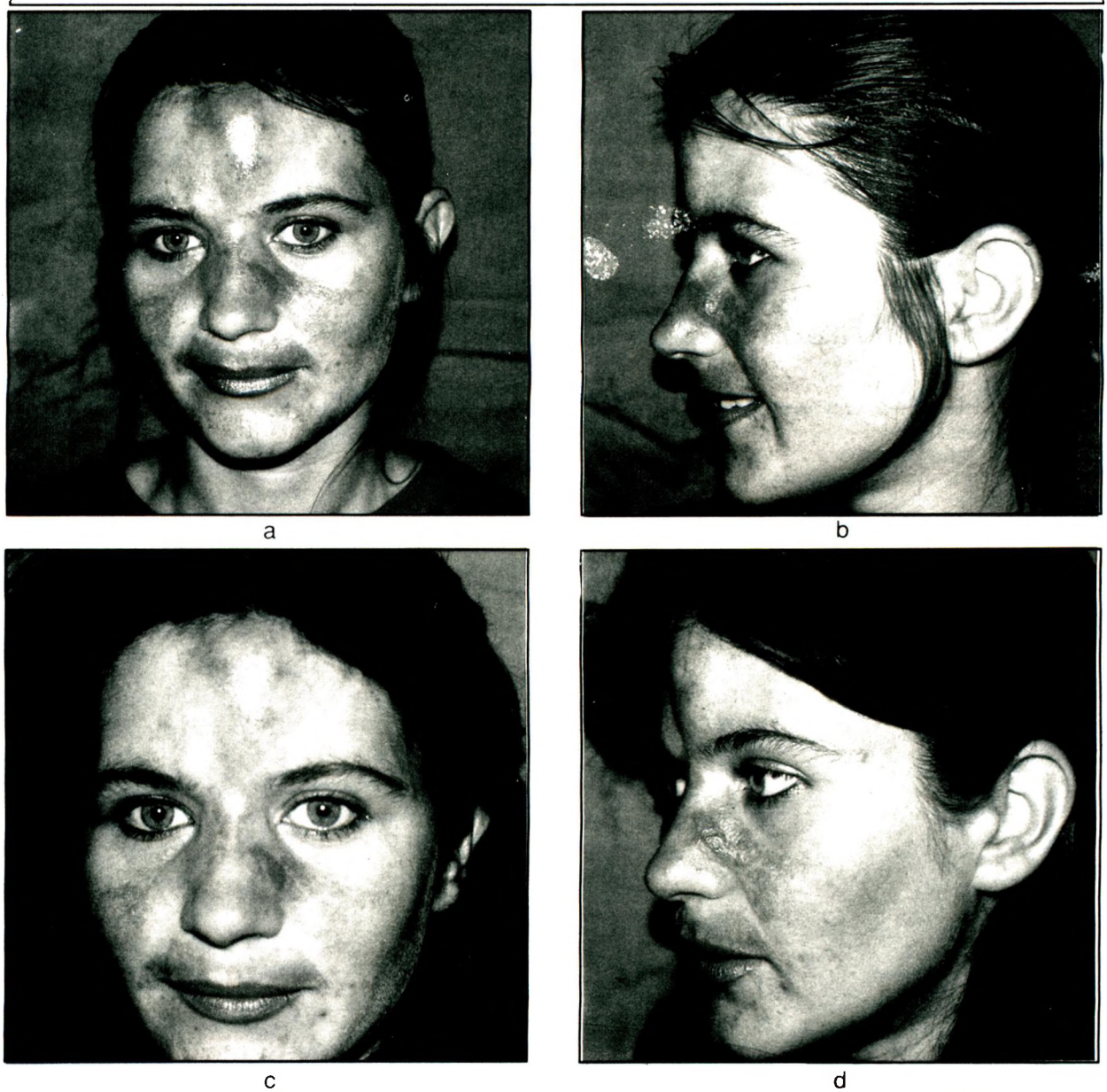

Fig 1. An 18 year old girl with hemangiomas on her forehead and left lateral nasal dorsum. (a) anterior, (b) lateral appearances before treatment. (c) Anterior, (b) lateral appearances one month after the treatment.

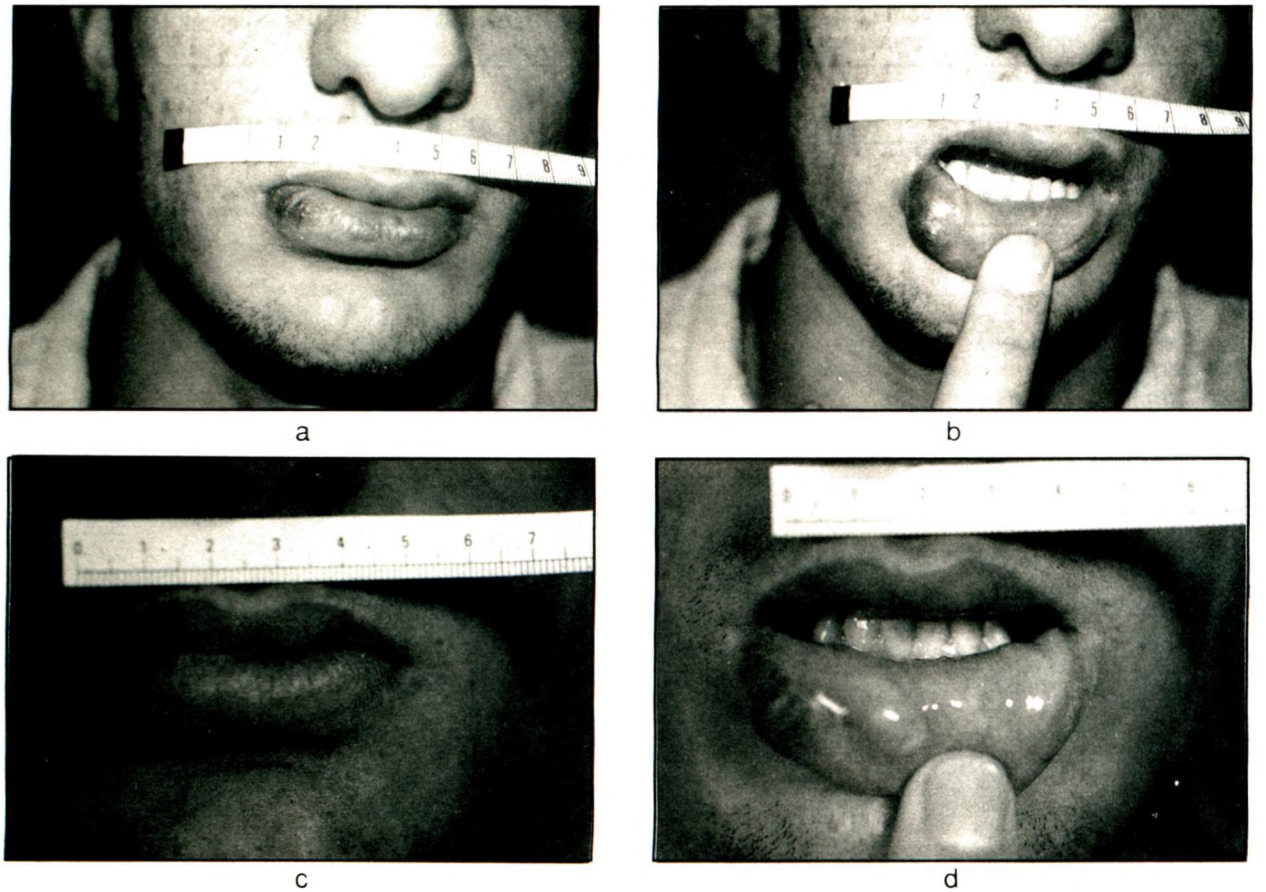

Fig 2. A 20 year old man with hemangioma on his lip. Appearances (a), (b) before treatment and (c), (d) one month after the treatment.

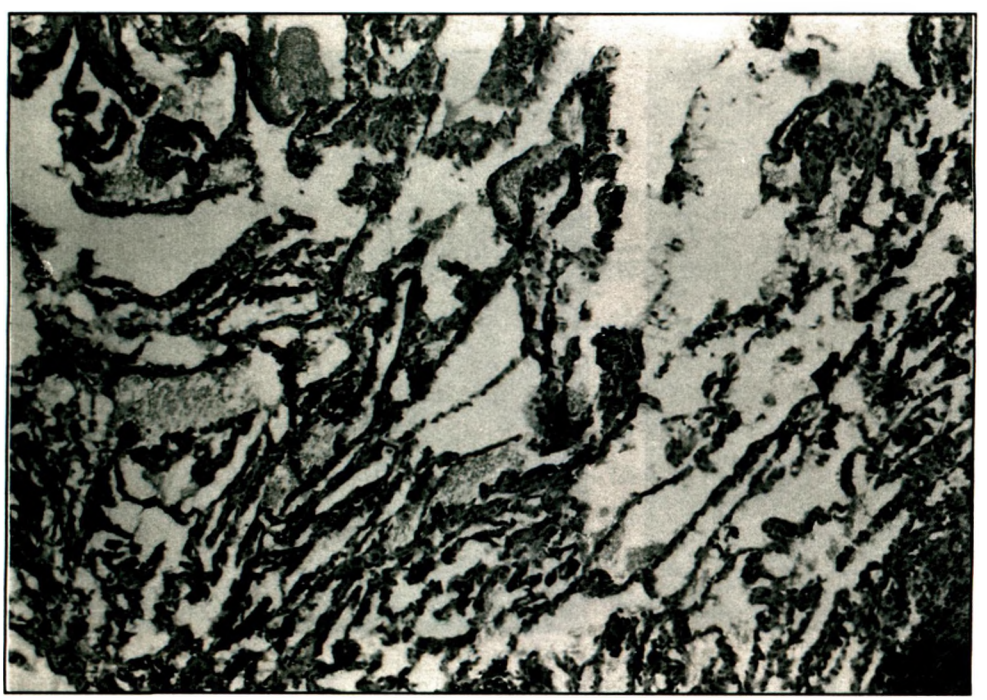

Fig 3a. Endothelial cell masses including wide cavernous structures were observed in the specimens harvested at the beginning of the treatment. HE X 50.

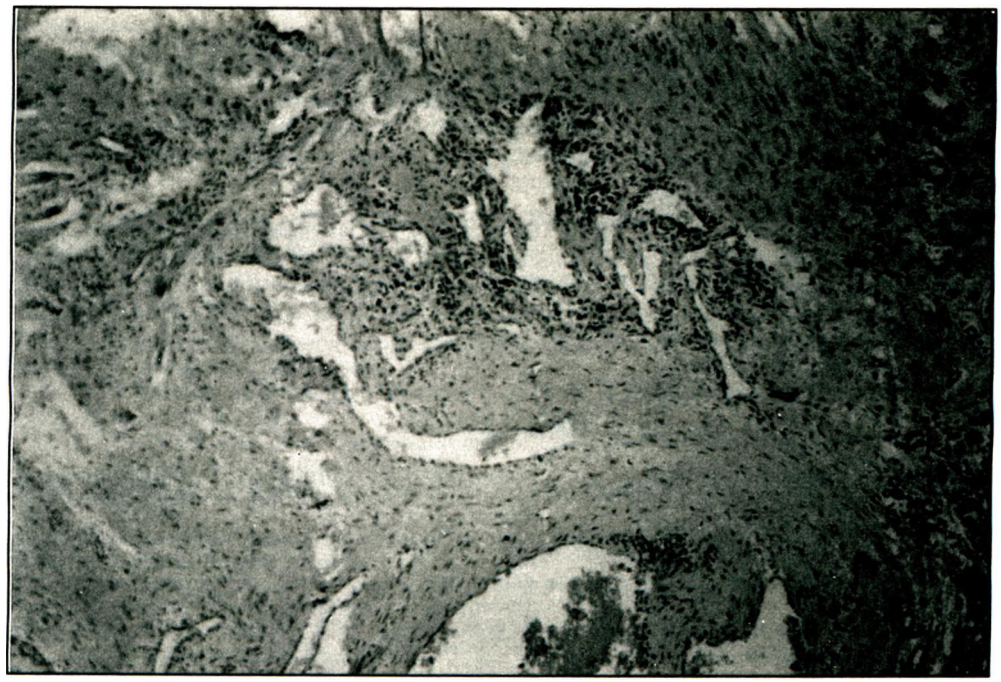

Fig 3b. Widespread fibrosis and hyalinization are shown in perivascular areas of specimen taken one month after the treatment. HE X 100

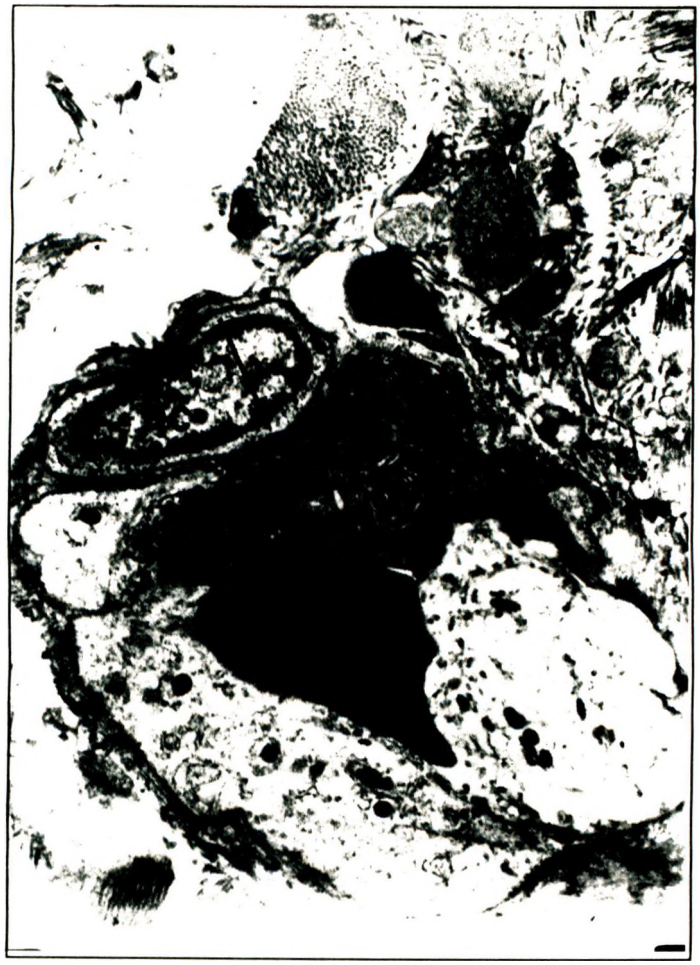

Fig 4. Electronmicroscopic view of a lesion taken one month after the treatment showing reduced capillary luminal spaces and endothelial cells projected into the lumens. (Arrow). Collagen fibrils accompanied by fibroblasts and macrophages were established all around the perivascular areas. X 6000.

DISCUSSION

Most hemangiomas are small, harmless birthmarks that involute to leave either normal or slightly blemished skin. Spontaneous involution arises the question " whether it is a real neoplasia or a hamartoma ". So, " wait and see" policy is the most realistic approach for these lesions. Capillary

hemangiomas usually stay in dermis or mucous membranes superficially and they can easily be subjected to traumas. So, they are often accompanied by ulceration and bleeding. It was determined that most of them could respond to corticosteroid therapy in some clinical studies (9). The results of alternative methods such as radiotherapy, embolization and compression have not been significant enough yet (10,11).

Less common type, cavernous hemangiomas stay in the deeper part of dermis and involve more mature cells. That is why they can involute less than capillary type. They form almost all the hemangiomas seen in adult life.

As the disabling hemangiomas are usually managed early in childhood, the lesions seen in adult life are mostly small ones making no problems other than bad cosmetic appearance and sometimes bleeding or ulceration. Moreover, they all, more or less continue irritating the patients themselves.

When treating adult hemangiomas, one must choose the simplest method causing minimal morbidity. Surgical excision can create deformities even if the lesions are quite small. In these cases, interferon therapy must be considered.

Interferon alfa-2a was developed as an antiviral agent, but it has also been shown that it could exert antitumour effects in experimental animals (12). Although the menchanisms of interferon antitumour action are not known exactly, the tumour vasculature may represent a single target. Thus, it has been shown in murine models that interferon can inhibit tumour induced angiogenesis and induce regression of subcutaneous transplantable tumours by damaging tumour vascular endothelium (13). It has been shown histologically in experimental animals that interferons cause delay in the initiation of proliferation of not only capillary buds, but also fibroblasts and to a lesser extent epithelium across traumatized regions. So, they do not inhibit wound healing but delay the process (14,15).

Ezekowitz et al, evaluated the effects of daily subcutaneous injections of interferon alfa-2a in 20 neonates and infants with life threatening hemangiomas that failed to respond corticosteroid therapy and observed more than 50% regression in 18 patients (16).

In this study, we tried to find out if the interferon therapy in adult nemangiomas was as effective as it was in infantile ones. It was known that inflammatory process included fibrosis with neo-argiogenesis. Interferon might have caused inflammatory reaction as other agents did, but as a difference, it had anti-angiogenic effect. In fact, intralesional application of interferon resulted in regression of lesions due to fibrosis and hyalinization without any angiogenesis in the study. We supposed that anti-angiogenicity is the difference which made the interferon more effective. As a result, fibrosis and hyalinization without angiogenesis might make the lesions smaller. In the study, all lesions became more acceptable for patients and their smaller dimensions encouraged the patients for a probable surgical excision at a later attempt.

Intralesional injection of interferon alfa-2a without any adverse effects other than fever can be considered as an effective method for the treatment of adult hemangiomas due to its ability to cause regression more than 20%.

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