CASE REPORT

Treatment of lymphangioma with alpha-2a-interferon

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Abstract

Objective: to describe the results of the use of alpha-2a-interferon in the treatment of inoperable childhood lymphangiomas refractory to other therapeutic management.

Method: we reviewed the literature about pathogenic events and the treatments available for lymphangiomas. Based on that, we used alpha-2a-interferon at a dose of 3 million units/m2/day administered subcutaneously to patients with inoperable disease and no response to other treatments. We conducted periodic clinical and laboratory control to evaluate the response and the adverse reactions to alpha-2a-interferon administration.

Results: we observed that the 6 patients with inoperable lymphangiomas who used alpha-2a-interferon had a satisfactory clinical response associated with minimum adverse reactions. Of these patients, 5 had partial regression of their lesions, and 1 remained stable.

Conclusion: alpha-2a-interferon may be one more available treatment for inoperable childhood lymphangiomas.


Introduction

The definition of lymphangioma, first described in 1828 by Redenbacher (apud Martinot, 1997),1 is still controversial today. Some authors define lymphangiomas as a congenital malformation of the lymphatic system,2-5 while others regard them as congenital hamartoma3,6 or benign vascular tumors caused by the proliferation of lymph vessels.7

The incidence of lymphangioma is relatively rare,1,6,8 and usually occurs during the first two years of life. The most frequently involved regions still include the head, and the neck, followed by extremities, trunk, and abdomen.3,4,7-9 This lesion is usually asymptomatic, becoming evident as a painless, cystic mass adhered to the deep planes, covered in normal skin, with slow growth and variable size.

Although histologically benign due to their infiltrative nature, lymphangiomas may expand into adjacent tissues and/or vital structures, causing some life-threatening complications.1,2,4,5,8,9 There are reports of spontaneous regression, however this is not common.

The involvement of the tongue is extremely rare, with concentrated or diffuse lesions. Most cases present diffuse lesions. The tongue assumes a granular appearance with multiple, transparent, lymph-filled cysts, occasionally causing these vesicles to bleed and become hemorrhagic. Tongue size is usually increased, presenting protrusion, dryness, and fissures, which may interfere with chewing, swallowing and speech, in addition to causing orthodontic anomalies and psychological disorders.3

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Several treatment methods have been proposed, including aspiration, incision and drainage (these methods may play an important role in emergency decompression, and are not regarded as definitive treatments), steroids, laser, chemotherapy, irradiation, bleomycin-induced sclerosis, 50% glucose, doxycycline, Ethibloc® or OK-432 and interferon alpha 2a (IFN alpha 2a). Some of these methods have unsatisfactory results and unacceptable complications.

Complete surgical resection has been preferred, however, due to the infiltrative nature of lymphangiomas, this procedure becomes incomplete and hard to use, and can only be applied in 10 to 50% of the cases. Therefore, recurrence becomes an important problem, with a prevalence rate between 0% and 27% after total exeresis and a prevalence rate between 15% and 53% after partial exeresis. Surgical complications, which occur in 19% to 33% of the cases, include formation of hematoma, lymphocele, scar, abscess, infection, wound dehiscence and nerve palsy.

Among sclerotizing agents, OK-432, a lyophilized mixture of Su protein of group A Streptococcus pyogenes, incubated with penicillin G, which was used to treat lymphangiomas initially reported by Ogita et al. in 1987. This drug had a response rate up to 92% with minimal side effects and no cicatricial damage to the skin. OK-432 is not commercially available in Brazil yet.

This article is about our experience with IFN alpha 2a in the treatment of progressive and irresectable lymphangiomas.

Patients and methods

Six patients aged between 23 days and 17 years (4 males and 2 females) who presented recurrent, irresectable and progressive lymphangiomas and received IFN alpha 2a, were studied (Table 1).

After confirming diagnosis through clinical examination (imaging and/or biopsy), patients were classified according to the proposal of Landing and Farber, who categorize lymphangiomas into three anatomical types: a) capillary lymphangioma or lymphangioma circumscription, corresponding to cutaneous vesicles with light-colored contents; b) cavernous lymphangioma, an ill-defined cutaneous or subcutaneous mass and c) macrocystic lymphangioma - when there are one or more cavities that are sufficiently large to allow echocardiographic images - and microcystic lymphangioma - with punctiform cavities (apud Balakrishnan, 1991). Patients with irresectable lesions received a subcutaneous dose of IFN alpha 2a at 3,000,000 U/m²/day. Only one patient received the drug 3 times a week since we had not defined the use of IFN alpha 2a yet. Those patients with associated hemangiomatous lesions received prednisone and epsilon-aminocaproic acid. Throughout the period in which patients received IFN alpha 2a, periodical hematological and biochemical tests, and control ophthalmologic examination were performed.

Response criteria followed the World Health Organization guidelines and were applied whenever possible: CR (complete response) - the whole lesion vanished for at least 4 weeks; PR (partial response) - the lesion reduced 50% or more for at least 4 weeks, without progression of any tumoral lesion and without formation of new lesions; SD (stable disease), a reduction of less than 50%, and an increase of less than 25%, and no new lesion; PD (progressive disease), increase of 25% or higher, or appearance of new lesions.

Discussion

Interferon alpha 2a has been used with excellent results in the treatment of hemangiomas. Reinhardt et al. (1997) assessed the efficiency of IFN alpha 2a in the treatment of two patients with irresectable lymphangioma, associated with pleural effusion. Both patients had good response, with improved symptoms and reduction in the number of hospitalizations, in addition to minimal side effects.

The IFN alpha 2a has a direct action in vitro, inhibiting the migration and proliferation of endothelial cells and other angiogenic steps. In vivo studies, conducted on animals, with lymphocytes and angiogenesis induced by tumoral cells, the IFN alpha 2a showed indirect action, inhibiting angiogenic stimulus through the inhibition of the effects of specific growth factors on the proliferation of endothelial cells.

Maddalozzo et al. (1999), based on the evidence that cystic hygromas, also known as cystic lymphangiomas, are characterized by the proliferation of small blood and lymph vessels, and considering that some malignant and benign tumors depend upon the unbalance between the angiogenesis inducers and inhibitors, postulated that cystic hygroma cells are angiogenic due to the increased secretion of angiogenic inducers that allow their proliferation. In their in vitro studies, they showed that the angiogenic activity of cystic hygroma cells occurred due to the increased secretion of bFGF (basic fibroblast growth factor), an angiogenic inducer, and low levels of TSP-1 (trombospondin-1), an angiogenic inhibitor. Therefore, they concluded that lymphangiomas may represent an angiogenesis-dependent neoplasia.

Six patients used and/or have been using IFN alpha 2a. The most frequently reported side effects included fever (max. 38°C), anorexia and fatigue, which disappeared a few days after the treatment was implemented and did not justify any change in the administration of the drug. None of the patients presented significant leukopenia and/or thrombocytopenia in the control blood tests; however, the biochemical test results of patient 5 revealed an increase in transaminase levels after the use of IFN alpha 2a for one
Table 1 - Clinical and treatment characteristics of patients with lymphangioma

<table>
<thead>
<tr>
<th>Pnt #</th>
<th>Patient Age</th>
<th>Gender</th>
<th>Race</th>
<th>Lesion Site</th>
<th>Lymphangioma classification</th>
<th>Associated signs and/or symptoms</th>
<th>Treatment</th>
<th>Intercurrent diseases caused by the treatment</th>
<th>Duration of treatment</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8to11m</td>
<td>M/W</td>
<td>M/W</td>
<td>Right cervical region</td>
<td>Cavernous</td>
<td>Capillary</td>
<td>02 surgeries†</td>
<td>INF 3,000.000 u/m²/d†</td>
<td>11m</td>
<td>PD</td>
</tr>
<tr>
<td>2</td>
<td>17yr</td>
<td>F/W</td>
<td>F/W</td>
<td>Tongue</td>
<td>Capillary</td>
<td>06 surgeries INF 3,000.000 u/m² 3x/wk*</td>
<td>Dyslalia 38°C fever in the 1st week</td>
<td>7m</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>23d</td>
<td>M/W</td>
<td>M/W</td>
<td>Thoracic wall</td>
<td>Macrocystic</td>
<td>INF 3,000.000 u/m²/d</td>
<td>37.8°C fever and irritation in the 1st week</td>
<td>6m</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2m</td>
<td>F/W</td>
<td>F/W</td>
<td>Sublingual Cervical region</td>
<td>Capillary upperairway compression</td>
<td>INF 3,000.000 u/m²/d OK432**</td>
<td>38°C fever, local inflammatory reaction in the 1st week</td>
<td>2m</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11to10m</td>
<td>M/Br</td>
<td>M/Br</td>
<td>Sublingual region Cervical bilateral and submandibular</td>
<td>Capilar</td>
<td>INF 3,000.000 u/m²/d</td>
<td>38°C fever for 4d and tiredness for 10d. Increase in GOT and GPT</td>
<td>7m</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3yr</td>
<td>M/B</td>
<td>M/B</td>
<td>Auricular, cervical, submandibular, left supra-clavicular regions, upper third of mediastinum anterius</td>
<td>Macrocystic</td>
<td>Upperairway compression, dyslalia, psychological disorders</td>
<td>INF 3,000.000 u/m²/d</td>
<td>38°C fever and tiredness in the 1st week</td>
<td>1 to 4m</td>
<td>PD</td>
</tr>
</tbody>
</table>

Ptnt= patient; Gnd= gender; B=black; Br=brown-skinned; W=white; M=male; F=female; yr=years; m=months; d=days; PR=partial response; SD=stable disease; PD=progressive disease; CRA=cardiorespiratory arrest
† 1 surgery in the cervical region and 1 in the tongue
* used concomitantly with epsilon-aminocaproic acid and prednisone, patient # 1 for 7 and 4 months, respectively; patient # 2 for 1 month
** Applied in 2 sessions after SD with use of Interferon-alpha-2a

Among the patients who received IFN alpha 2a, only patient 4 did not have any reduction in lesion size. We can neither assume that this is due to a failure in the therapy, since the lesion did not show any progression, nor discard the possibility of IFN alpha 2a ceasing or reducing the progression rate of the disease (the response was classified as SD). Two applications of OK-432, whose response was satisfactory, were used as treatment complementation. All of the remaining 5 patients had a partial response. All lesions in patient 5 disappeared except the sublingual one. After the first month of treatment, and after the administration of IFN alpha 2a was changed to alternate days, the lesions reappeared in 15 days due to an increase in transaminase levels. At present, this patient uses IFN alpha 2a on a daily basis, and has only a sublingual lesion and no change in the

month (pre-treatment, GOT 25.0 IU/l and GPT 34.5 IU/l; control, GOT 134.7 IU/l and GPT 160.2 IU/l). In this case, medication was administered on alternate days until the enzymes reached their normal levels again, which happened within 15 days.
transaminase level. Patient 6 showed some improvement after the cessation of mediastinal infiltration and a reduction in upper airway compression and, as a result, initial breathing workload was minimized.

Patients 1 and 2 received prednisone and epsilon-aminocaproic acid. The use of these drugs was based on the evidence of associated hemangiomatic lesions. Prednisone, commonly used in the treatment of hemangiomas, would function as an angiostatic steroid in angiogenesis, by blocking estrogen receptors (abnormally larger in hemangiomas) and inhibiting angiogenic factors. This could be advantageous to our patients as far as hemangiomatic lymphangiomas are concerned. The epsilon-aminocaproic acid would interfere with the fibrinolytic mechanism, whose activation inside the hemangiomas would prevent thrombosis, and would also avoid the dissolution of thrombi formed in the microcirculation of hemangiomas. As these patients did not present any apparent advantage over those exclusively treated with IFN alpha 2a, the use of these drugs was discontinued.

Considering the IFN alpha 2a mechanism of action on angiogenic lesions, the results obtained by Reinhardt et al. through the use of IFN alpha 2a on two patients with lymphangioma, the recent results presented by Maddalozzo et al., who showed an angiogenic activity in lymphangiomas, and the results obtained through the use of IFN alpha 2a in our patients (even though none of them had a complete response), we suppose that IFN alpha 2a has a crucial role in the treatment of these lesions, with minimal side effects, and can be used as a therapeutic weapon against lymphangiomas, especially in patients with irresectable or life-threatening lesions or in cases in which surgery would be mutilating.

We have to consider that most of our patients presented a slow and gradual response to the treatment. The lack of response within the first weeks of treatment may not be interpreted as therapy failure. The assessment of treatment responses should be carried out carefully, since multicystic lesions in which these cysts are communicating may have different dimensions due to the transfer of variable amounts of contents among cysts.

Many questions as to the ideal dosage, length of treatment, anatomical type with better response, and mechanism of action of IFN alpha 2a remain unanswered. Therefore, several studies are still necessary to confirm our results.

References