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Intralesional Injection of Bleomycin - First Choice as Treatment Option for Lip Hemangiomas

KEYWORDS: lip hemangioma, non-surgical treatment, Bleomycin, intralesional injection

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ABSTRACT *Bleomycin is a cytotoxic substance discovered about 50 years ago and successfully used today in multiple chemotherapy of some human cancers, but in the last 20 years it has proven its usefulness in the local treatment of some benign lesions (for example, intralesional injection of the vascular tumors). In this paper we present the clinical case of a female patient diagnosed with a hemangioma of the lower lip at the age of adulthood, where two intralesional injections with a solution of Bleomycin were performed at one month interval between them, with very good aesthetic and functional results, only three months after starting therapy. In our opinion, lip hemangioma location requires choosing a treatment method which primarily avoids the facial mutilation and optimally restores the lip functionality, without hurting the facial aesthetics, therefore we consider Bleomycin intralesional injection as first choice therapeutic option to treat lip hemangiomas. When Bleomycin is injected intralesional in lip hemangiomas in much lower doses than those used in systemic chemotherapy of cancer, it will involve minimal side effects and therefore it is a safe substance for the treatment of these injuries, despite its general cytotoxic characteristics.*

INTRODUCTION

Bleomycin, an antibiotic with anticancer activity, is a cytotoxic mixture of polypeptides with antibacterial, antiviral and antitumor properties, which was isolated in the early 1960s from a soil fungus (Streptomyces verticillus) by Umezawa and colleagues from Institute of Microbial Chemistry in Tokyo [1]. This cytotoxic glycoprotein mixture can be separated by chromatography into two main fractions: A and B, which in turn can be separated into A1-6 and B1-5 subfractions, by chromatography too [2]. In the center of the molecule there is a complex structure able to bind to metals, coupled with a tripeptide chain and a terminal bithiazolic carboxylic acid. Bleomycins differ between them only by terminal amine, which can be modified by changing amines that add to the fermentation medium. Both toxic and antitumor action of various bleomycins produced by fermentation varies notably among them, the mixtures of bleomycin A2 (Bleomycin) and B2 or bleomycin A5 (Pingyangymycin) being commonly used in clinical practice [3].

The main mechanism of Bleomycin's action consists of: DNA cleavage by free radicals that are formed when the Bleomycin's core is oxidized, the inducing of apoptosis in rapidly growing cells, the sclerosing effect on vascular endothelium, the degradation of cellular RNA and inducing of tumor necrosis factor [4].

Bleomycin has attracted significant interest in oncology because of its antitumor activity in squamous cell carcinoma of the head and neck, Hodgkin and non-Hodgkin lymphomas and testicular carcinomas [5]. Its immunosuppressive and myelosuppressive activity is low and toxicity does not overlap with that of other drugs, that's why Bleomycin won such an important role in the treatment of cancer by combined chemotherapy. The side effects of Bleomycin, mainly pulmonary and cutaneous ones, are because hydrolase that degrades this substance is found in various normal human tissues (such as liver) but has low activity in the lungs and skin.

Over time, besides the excellent activity of Bleomycin systemically administered in the treatment of cancers mentioned above, there were published successful results of this cytotoxic substance's incorporation in dermatology therapeutics, as intralesional injection or its topical use for: warts, skin cancers, oral leukoplakia, Kaposi sarcoma, keloid lesions, hemagiomas, cystic hygromas [3].

Based on these encouraging results, we briefly present a clinical case that we had under observation and a synthetic review of the medical literature regarding the use of intralesional injection of Bleomycin as the first therapeutic option for lip hemangiomas, a benign pathology requiring the avoid any aesthetic or functional consequence of ablative surgery.

CASE REPORT

A female patient of 35 years old, without personal or familial medical history, addressed to the Clinic of Oral and Maxillofacial Surgery in Iasi presenting a deformation in the thickness of the ½ left lower lip (**fig. 1**) through an imprecisely delimited tumor, with soft and depression consistency, painless, about 4 cm in diameter, with the mucosal lining covering of purple color (**fig. 2**). The patient said that she had this tumor since childhood, arguing the current addressing for medical advice due to aesthetic reason but also because of tumor growth's accelerating in the last two months. Clinical objective examination diagnosed a hemangioma of the lower lip and intralesional Bleomycin injection was decided for treatment. Under local anesthesia, it was performed perilesional and intralesional injection of Bleomycin medac (1 vial of powder Bleomycin medac with 15,000 IU, dissolved in 5 ml saline, yielding a concentration of 3 mg / ml active substance, that was injected intralesional in dose of 0.25 mg / kg body weight in the

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first session), reprising the procedure with the same dose of substance after a month, when the patient presented with a significant remission of the tumor volume (**fig. 3** and **fig. 4**). To combat the local discomfort, pain and edema after the procedure performed, the patient received Dexamethasone (8 mg, 2 ml = 1 vial), 1 vial i.v. X 3 / day (at 8 hours), 3 days. The clinical assessment performed after 3 months of the first hospitalization, after two intralesional Bleomycin injections at intervals of one month, found the total regression of the lower lip hemangioma. Please note that the procedure was performed under informed consent of the patient and after it ruled out a possible pregnancy evolving, taking into account the cytotoxic quality of the substance used in treatment.

DISCUSSION

Vaso-forming tumors were classified in 1982 by Mulliken and Glowacki, a pattern-accepted today, which divides its into two broad groups: hemangiomas and vascular malformations [6]. Hemangiomas are identified as vascular tumors with rapidly proliferating endothelial cells which shrinks over time. All other vascular anomalies are malformations, resulting in abnormal development of vascular plexus. Malformations have a normal growth cycle of endothelial cells (affecting veins, capillaries and lymphatics) and do not regress. Hemangiomas usually appear within the first month of life, develop a rapid proliferative phase and then slowly regress to near complete resolution. In contrast, vascular malformations are more stable over time and do not regress.

Hemangiomas of oral cavity are not common pathologic entities; many real hemangiomas regress in time but 10-20% of them regress incomplete and may present complications requiring treatment [7]. Hemangioma's diversity (in terms of location, size, blood flow, ability to proliferate) explains different therapeutic attitude in addressing these pathologies. That's why sometimes surgical treatment is indicated, sometimes it requires medical management, as there are situations that require combination of medical with surgical procedures or, conversely, there are cases where no treatment is recommended.

The clinical examination and medical history of the case presented in this paper, allowed us the diagnosis of „Lower lip hemangioma", which after a long period of stagnation appeared to enter in a new proliferative phase (probably accelerated by a minimum local trauma). The patient age and location of this benign vascular tumor in a region with significant implications in facial aesthetic motivated our therapeutic orientation to a non-surgical method, but also safe and with a high rate of favorable response.

Medical therapies have become the mainstay in the management of many hemangiomas, the major objectives of the treatment for these injuries being: a) prevention of life-threatening complications or complications that interfere with normal function and treatment of such complications if its arise; b) prevention of mutilation; c) minimization of psychological stress; d) avoiding potentially aggressive scarring; e) minimization of scarring, infections and pain after treatment [8]. Besides surgical management (classical or laser surgery), cryotherapy, systemic or local administration of corticosteroids, lip hemangiomas may benefit from sclerotherapy with antiangiogenic drugs, which inhibit the formation of neovasculature or induce apoptosis of endothelial cells; Triamcinolone, Dexamethasone, Prednisolone, Interferon, Cyclophosphamide, Vincristine, Bleomycin are some drugs used for this purpose [8]. We chose Bleomycin due to good results with this substance in the treatment of facial hemangiomas in the last 7 years in our surgical service.

Bleomycin, an effective anticancer antibiotic in many malignant tumors found in humans, has also been reported since 1990s as an effective form of treatment for large or complicated cutaneous hemangiomas in children [9, 10]. Subsequent studies have shown that intralesional Bleomycin induces an accelerated resolution in patient's hemangiomas without signing severe complications [11, 12]. Intralesional injection of Bleomycin in small doses are frequently used in China as a sclerosing agent for the treatment of vascular anomalies and has been cited as effective treatment option for infantile hemangiomas with good results in terms of patient safety [13]. In a prospective study undertaken by „Pretoria Vascular Malformation Study Group", Bleomycin administered intralesional proved to have a curative effect on infantile hemangiomas, with fewer side effects, the main complications reported were local pain and transient „flu-like" symptoms [11]. Another study, conducted by „Red Cross Children's Hospital" in South Africa, showed that Bleomycin was effective in accelerating regression of hemangiomas in infants, with a success rate of over 70% in thirty patients treated, hyperpigmentation being the only reported side effect [12].

Bleomycin has also been reported to be effective in treating hemangiomas when administered in combination with Dexamethasone. In a group of 21 patients in whom hemangiomas have been treated with this combination of drugs, it has been reported a reduction in tumor size greater than 90% to over 80% of treated patients. Although efficacy was largely attributed to Bleomycin, given the fact that both drugs were administered at the same time and considering that the two drugs have previously been shown to inhibit angiogenesis in human hemangiomas, the degree to which each drug helped inducing tumor regression is not clear [14]. In our case, the anti-inflammatory drug (Dexamethasone) was systemically (intravenously) administered, to not making lip deformity by injecting too much sclerosing solution.

In vitro studies on human hemangiomas biopsy pieces showed that Bleomycin can inhibit the growth of hemangiomas in human patients, largely by neovascular inhibition [15]. This is confirmed by the observation that Bleomycin inhibits growth factor-induced endothelial cell invasion, endothelial cell growth and also induces endothelial cell apoptosis [16]. In addition, increased apoptosis coincides with regression of hemangioma. Thus, the induction of apoptosis by Bleomycin and its inhibitory action on angiogenesis form the basis of therapeutic effect for this drug in hemangiomas [17].

Used alone or in combination with a corticosteroid preparation (Dexamethasone or Triamcinolone), the effectiveness of intralesional Bleomycin injected is based on powerful sclerosing effect on vascular endothelium, which makes it more effective in cases of proliferating infantile hemangiomas, by inhibiting proliferation [11, 18].

Analysis of plasma concentration after 1 mg of Bleomycin intralesional injection showed a peak after 45 minutes ranging from 7.1 to 113.5 ng / ml, which decreased from 4.9 to 34.8 ng / ml after 2 hours [19]. The difference found between patients is due to molecule fragmentation and its subsequent distortion and a greter capacity of plasma degradation in some people. While it is true that 1 mg of

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Bleomycin injected is far from many of the doses used in cancer chemotherapy, a plasma concentration of 113 ng / ml is not different from that seen in patients receiving antineoplastic doses in slow infusions. Even at 120 minutes after injection plasma concentrations are low, there is a systematic exposure to Bleomycin, so that Bleomycin should not be administered to women of childbearing age, without excluding the possibility of pregnancy. Although this risk is more theoretical, we also had concerns regarding the exclusion of pregnancy in our female patient of 35 years old.

Bleomycin sulfate is stable at a pH range between 4 and 10, so no degradation occurs when it combined with 0.9% saline solution or 1% lidocaine hydrochloride, when the pH varies between 5 and 7 [20].

Use of intralesional Bleomycin injected in hemangiomas with good results was documented and reported in the literature after 1990s. Zheng published the results of treatment with intralesional Bleomycin A5 injected in children with hemangiomas, noting a success rate of over 90% [21]. Sarihan obtained similar results in the treatment of complicated hemangiomas [10]. Kullendorff treated five children between 5 and 19 years old with extensive and inoperable hemangiomas, using 2 mg of Bleomycin intralesional injection administered as a solution of concentration 0.4 mg / ml, injected for 6-10 times at interval of 4-10 weeks [9]. In all cases, the complete resolution of the pain and a partial reduction of the hemangioma volume were noted and no complications or side effects were reported. In our case, the minimal side effects recorded after each of the two sessions of intralesional Bleomycin injection have contributed to the psychological comfort of the patient, she saying she was very satisfied with the result only three months after the first admission.

The data published in the literature in the last 20 years on treatment's outcomes in hemangiomas conclude that there are three non-surgical procedures (systemic or intralesional corticosteroids, Bleomycin intralesional injection and Propranolol systemically administered) that may be useful in the management of proliferating hemangiomas. Each method has advantages and disadvantages: a) the rate of response to steroid therapy systemically administered is about 30-90%, but with signaling the inherent side effects of corticosteroids [22]; b) intralesional injection of corticosteroids showed a response rate which is not constant, with a 50% reduction in the volume of hemangioma in only one third of cases [23, 24]; c) systemic administration of Propranolol is for a period of 3-9 months, with cardiology surveillance due to potential side effects of hypotension, bradycardia, hypoglycemia [25, 26]; d) intralesional injection of Bleomycin requires several sessions and treatment is done under general anesthesia in children's cases [12]. Of all the non-surgical methods applied in the treatment of hemangiomas, intralesional injection of Bleomycin (which can be combined with Triamcinolone) is the method that has the highest success rate [27, 28, 29, 30]. The most important complication of systemic therapy with Bleomycin, the pulmonary fibrosis, has not been reported after intralesional injection of Bleomycin.

CONCLUSIONS

Although Bleomycin is a cytotoxic agent used systemically in chemotherapy for malignant tumors in humans, intralesional injection of Bleomycin in lip hemangiomas is a safe and local non-surgical method of treatment.

Intralesional injection of Bleomycin in lip hemangiomas as first choice is motivated by the high success rate of the method (due to Bleomycin's strong sclerosing effect on vascular endothelium) and the absence of procedural scars.

The side effects of intralesional Bleomycin injection are minimal: local swelling, discomfort, adjacent skin congestion, possible nausea and decreased appetite, but its usually resolve in a few days or weeks, with or without symptomatic treatment.

Fig. 1. Left half of the lower lip's hemangioma (extraoral image)

Fig. 2. Left half of the lower lip's hemangioma (intraoral image)

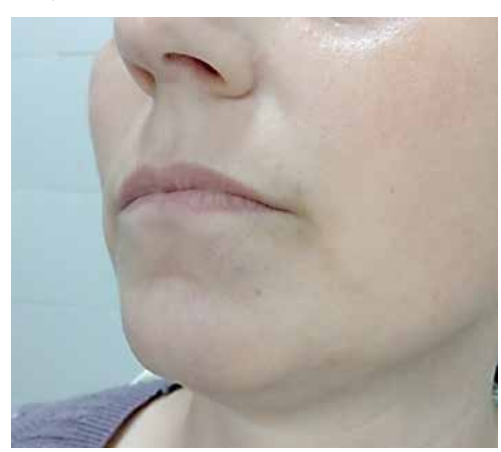

Fig. 3. Left half of the lower lip's hemangioma, after a month of intralesional Bleomycin injection (extraoral image)

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Fig. 4. Left half of the lower lip's hemangioma, after a month of intralesional Bleomycin injection (intraoral image)

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