Primary Cutaneous Ewing´s Sarcoma: A Rare and Deadly Tumor. Case Report and Literature Review

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Abstract: *Introduction*: Ewing´s Sarcoma (ES) is a neuroectodermic tumor that rarely occurs on skin. In 85% presents in bones, and another 15% in extraskeletal tissue. It is the second most common bone cancer in children. ES has an incidence of one case per million per year, and the average age of presentation is 15 year-old. Extraskeletal ES has low frequency, and has been described at the para-spinal region, thoracic wall and lower extremities.

Objective: To report a low frequency clinical case, with controversies in its classification.

Clinical Case: A 79 year-old male with previous frontal basal cell carcinoma (BCC) history, assists to our department because of one-month evolution nasal tumor, which appeared the novo. The lesion was approximately 18 millimeters in diameter, with a 10 millimeters base, erythematous, firm to palpation. The histopathology demonstrated an Ewing´s sarcoma. The tumor had an extremely aggressive behavior, presenting local metastasis prematurely.

Conclusion: Thereby, we present a case of cutaneous Ewing´s sarcoma in an older adult with an aggressive behavior. The superficial cases of Extraskeletal Ewing´s sarcoma are exceedingly rare, and the majority is reported as a unique and small firm mass.

Keywords: Ewing´s sarcoma, cutaneous, extra-skeletal.

INTRODUCTION

The Ewing´s sarcoma family of tumors (ESFT) is a group of tumors of aggressive behavior that occur mainly during childhood. The ESFT includes the following entities: The classic or bone Ewing's sarcoma (ES), Extra-skeletal ES, Askin tumor of the chest wall and Peripheral neuroectodermal tumor (PNET) [1].

ES is a primitive neuroectodermal tumor, involving most frequently the bone, predominantly in children, affecting predominantly flat bones (pelvis and shoulder girdle), but may also involve diaphysis of long bones and rib cage [2, 3].

Classic ES represents less than 10% of all malignancies. It is the second most common bone cancer in children, after osteosarcoma. The peak incidence is 15 year-old, being one of the record aggressive tumors, with a high metastatic rate [3]. In recent years there have been great advances in knowledge of the epigenetics, hystogenesis and morphogenesis [2], and it has been proved that it originates from poorly differentiated mesenchyme cells [3,4].

Esiashvili et al., followed up patients diagnosed with Bone (Classical) ES between 1973 and 2004. The age of diagnosis was between 1 and 19 years old. It showed an incidence of 2.93 cases per 1,000,000 inhabitants per year in the United States, with a rate of metastasis from 26 to 28%. Overall survival rate at 5 years was 68% for located tumors, and 39% for metastatic disease [4]. This matches roughly with the study of classic ES by Kelleher *et al*., a few years later (2012), who reported a survival rate at 5 years of 70% approximately in non-metastatic disease, and less than 20% for those with recurrent metastatic disease [5].

Approximately 15% of the ESFT are located in soft tissue, in cutaneous or muscle tissue, this are denominated Extraskeletal ES [3]. Extraskeletal ES includes paravertebral soft tissues, skin, chest wall, and proximal extremities tissues, kidney, bladder, lung, prostate and meninges [3,4]. Rarely originates in deep soft tissues (subcutaneous) and even more exceptional skin superficially [2, 3].

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E-ISSN: 2310-998X/17

According to literature, Primary Cutaneous Ewing's Sarcoma (PCES), as well as the one originated in soft tissues, are entities of very low frequency [1,2,6]. There were 78 cases reported until 2011 [6], which are generally in the second decade of life and with statistically proven predominance in white women [1,2,6]. According to Molina *et al*. in March 2016, there were less than 100 reported cases [7].

Clinically the PCES has been described as a single lesion [2,8,9], soft, circumscribed, painful in some cases, fast growing, with an average time of evolution of five months, affecting deep dermis or cellular subcutaneous tissue [2,10] generally not adhered to deeper layers [10].

The PCES is difficult to diagnose because its low frequency and lack of clinical suspicion, therefore being under-diagnosed [2]. The diagnosis is made by histopathology, immunohistochemistry and cytogenetic, observing characteristically small round cell with CD 99 positive staining [2].

The prognosis for classic ES is still very unfavorable in children and adults, despite the therapeutic advances and aggressive management of this condition. It has been reported that the prognosis of PCES would be better, probably due to an early diagnosis regarding deep sarcomas, as it is more superficially, being easier to diagnose [1, 2].

We report a case of PCES, histopathology confirmed, with a very aggressive evolution, along with a review of the literature.

CLINICAL CASE

A 79 years-old male patient with a history of glucose intolerance, hypertension and chronic kidney disease stage II. Initially he consulted by a frontal tumor whose excisional biopsy showed a pigmented basal cell carcinoma, without committed edges, with adequate clinical and histopathology correlation. Six months later, in a routine control, refers concerns about the appearance of a new lesion of rapid growth, about month of evolution, located in the nasal dorsum. Physical examination highlighted one, unattached, slightly erythematous, with telangiectasia on the surface of 8 mm in diameter (Figure **1**) solid tumor; no other findings that might be relevant (without local lymph nodes or remote). Dermoscopy showed a lesion without pigment, erythematous, with slightly lighter or luminous center, clearly defined by multiple telangiectasia of radiated arboriform distribution was observed. These, in their genesis, circumscribe the tumor edge, becoming thinner as they approach the lighter center (Figure **2**). A differential diagnosis of BCC, keratoacanthoma and adnexal tumor was debated, so histopathology study was requested, performing incisional biopsy.

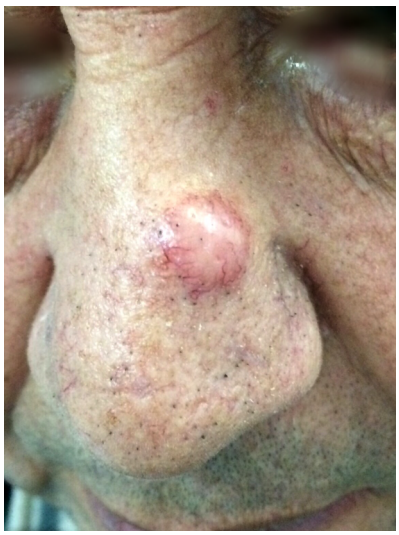

Figure 1: Nasal tumor 1 month of evolution.

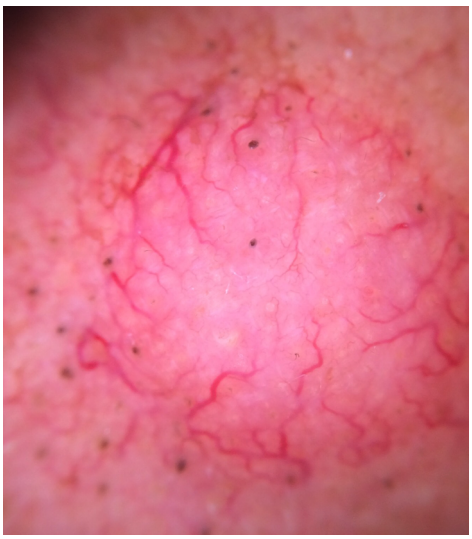

Figure 2: Dermoscopy of nasal tumor lesion, 1 month of evolution.

Histological examination showed a tumor of small round basophilic cells with scant cytoplasm, spherical core and fine chromatin arranged in sheets throughout the thickness of the dermis, without epidermal engagement compatible with a malignant neoplastic cells called "round and blue small cell tumors", as shown on Figures **3-4**, with hematoxylin eosin staining with 20x magnification and with 40x magnification

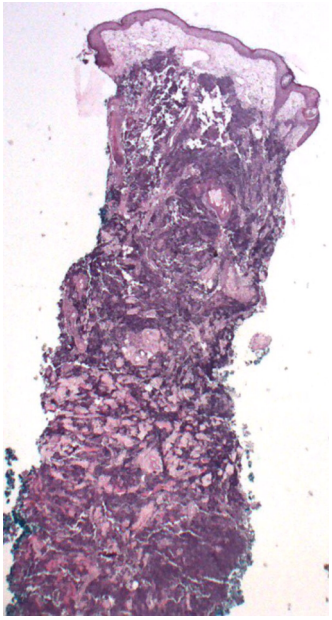

Figure 3: H & E stain at 20x magnification, shows commitment of the entire thickness of the dermis is observed.

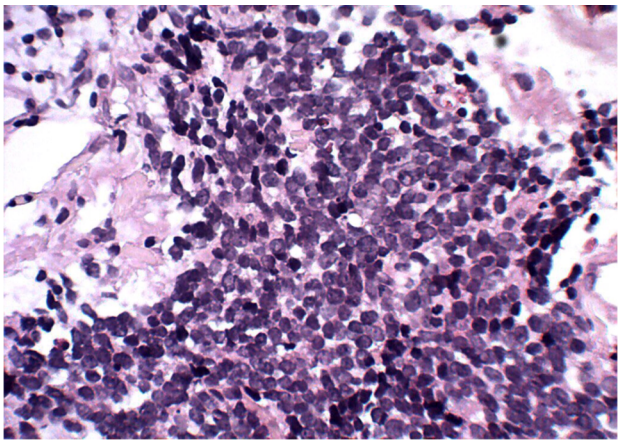

Figure 4: H & E stain at 40x magnification. The presence of small round cell tumor within the dermis and an intact epidermis are shown. Histological examination showed a tumor of small basophilic cells with little cytoplasm, and prominent nuclei and chromatin, arranged in layers through the entire thickness of the dermis, without epidermal engagement compatible with malignancy-called "small round and blue cells tumor".

respectively. The immune-histochemical study was strongly positive for CD99 (Figure **5** 40x), synaptophysin (Figure **6** 40x) and neurospecific enolase (Figure **7** 40x). Moreover, cytokeratin, chromogranin, Melan A, CD45, S100, CD20, CD3 and TTF were negative, completing the study for the correlation of PCES. The patient showed a rapid evolution in less than 30 days after the biopsy period. The tumor showed a sharp growth, expansionary, achieving a size of 25 mm in diameter (Figure **8**), becoming painful and slightly more friable, associated with higher secondary adherence to local invasion, highlighting in its evolution multiple palpable lymph nodes in the neck. A computed tomography (CT) with head and neck contrast was requested immediately, which demonstrated commitment of both cervical lymph node chains.

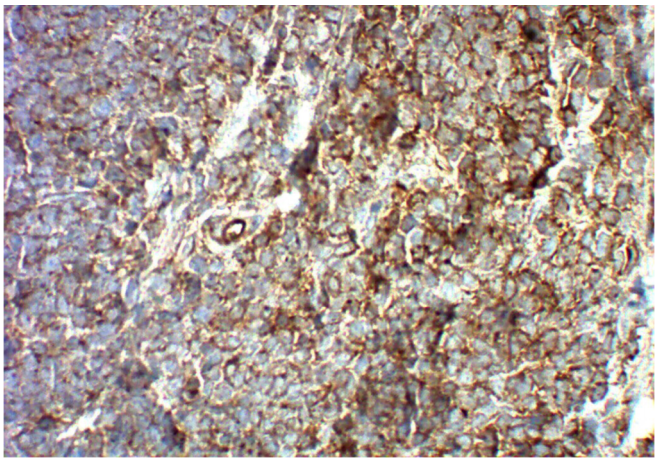

Figure 5: Immune-hystochemical study was intensely positive for CD99. Histopathology photograph with 40x magnification.

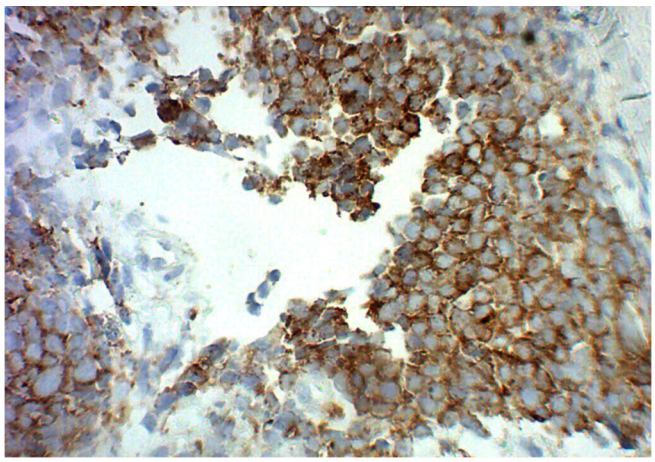

Figure 6: The study was positive for synaptophysin, histopathologic photograph with 40x magnification.

The patient was referred to oncologist surgeon, where a wide excision of the tumor associated with cervical lymph node dissection was performed, and died a few months after his intervention.

DISCUSSION

ES was first described by Ewing in 1921, as a malignant bone endothelioma. Angerwall and Enzinger in 1975 recognized that this same tumor could also occur in deep soft tissues and very rarely in the skin [5,6]. As mentioned previously, classic ES and PNET have varied in their definition over time, but thanks to

current research we know that clinically, morphologically and genetically, they share many characteristics, being today considered same family tumors [2,9].

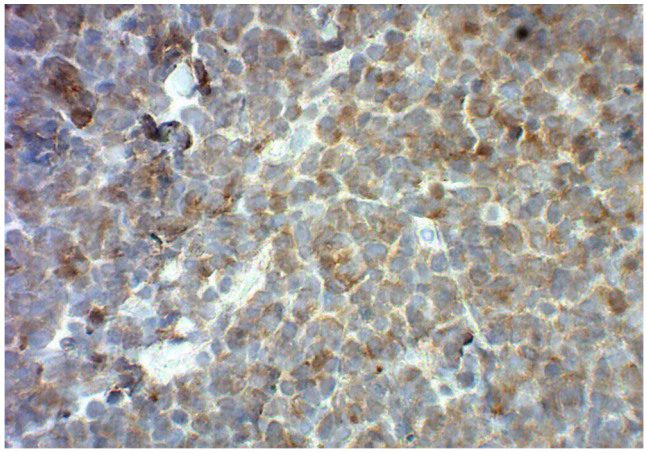

Figure 7: The study was positive for neuron-specific enolase, histopathologic photograph with 40x magnification.

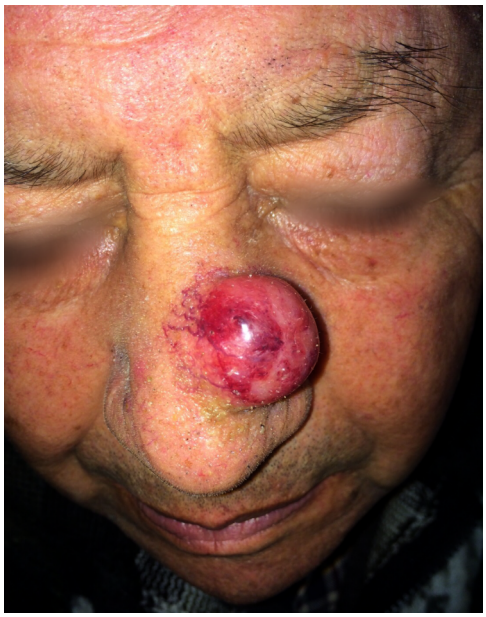

Figure 8: Nasal tumor, 2 months of evolution, which showed a rapid and aggressive growth, reaching 25 mm in diameter.

PCES it is a clear cell neuroectodermal tumor, an extremely rare condition, with very few cases reported in the literature [2,7,9]. It is most prevalent in children and young adults, so it is even more exceptional the presentation in an older adult, as the case exposed [2,7].

Because there are only a few reports in the literature of PCES, one systematic review is the Delaplace *et al*. review in 2012, with 61 patients. The average age of presentation was around 17 years (range 2-77 years), versus 14 years for bone (classic) ES [1]. The average presentation size of the tumor was 2 to 3 cm (range from 1 to 12 cm) [1]. The most common site according to this publication was in lower extremities (38%), followed by upper extremity (26%), head (20%) and trunk (16%). In addition, the PCES had a higher prevalence in women versus bone ES, which proved to be more common in men (33% of PCES were in men). This agrees with the findings of other studies that have suggested a higher frequency in women [1,2,7]. Delaplace described in this study, that tumors with volumes of over 200 ml were associated with poor prognosis [1]. This is why it is very important to suspect this entity to make an early diagnosis. In the case exposed, although it presented a lower volume at the diagnosis, it progressed aggressively, with regional metastases, in contrast to some reports where these low volumes tumors have a low rate of metastasis. This could be explained by tumor type or cytogenetic alterations were more aggressive in nature, a fact that was not reached to study due to the death of the patient.

Regarding to affected sites of extraskeletal ES, the most common soft tissue is the paraspinal, and subsequently the chest wall or soft tissues of lower limbs, however, it also can be presented in superficial ways, but much less often, either primary or as metastasis from a deeper tumor [2]. There are less frequent locations such as the feet [2], or vulvar region [13], or scalp [7], but found no case that was described on the face, and even less nasal dorsum as our patient, showing that would be extremely rare.

In the most recent reviews literature by Grasetti *et al*. in 2012 [2], it was established that extraskeletal ES types continue with very low prevalence. Generally, when they are limited to skin and soft tissue, they are clinically shown as a single small circumscribed lesion located in the mid to deeper dermis or subcutaneous tissue [2].

Collier *et al*., made a report of two cases plus a review of 76 cases reported in the literature for PCES [6]. In this case series, only two patients presented at diagnosis with metastases, and 8 patients developed them during follow-up group in which our patient would be categorized. Of the patients studied, 90% are alive, despite the different regimes of treatments performed. Treatments consisted of surgical resection and/or radiotherapy with shortened chemotherapy.

The most recent publication of PCES was a case report and review of the literature performed by Molina

et al. in March 2016, which specifies that the World Health Organization classifies it as a tumor of small round cells, with varying degrees of neuroectodermal differentiation, which occurs more frequently in the shaft of long bones of children and adolescents, but it can also occur in soft tissue and rarely in solid organs and skin [7]. This study corroborates that, like its bone counterpart, it also presents the molecular alteration who consists in the translocation of the long arm of chromosome 22q12 [7]. Highlighting that as the diagnosis of this tumor is very difficult at skin level, genetic diagnosis with the polymerase chain reaction (PCR) or fluorescence in situ hybridization, could be of great help to complement histology. It reiterates that would be more common in women and the age range is from 2 to 77 years, but most occur in the second decade of life. According to the publication, the most common site occurs in the lower extremities, and lesion size varies between 1 and 12 cm in diameter. It reports that a small single lesion with short time of evolution would represent classical presentation, with no evidence of metastasis. They propose that the best outcome would probably be given by surface location, which as we noted, would allow early diagnosis [7]. This publication mentions the study by Delaplace *et al*. [1], describing a probability of 10-year survival rate of 91% for PCES, in contrast to the survival rate of 68% at 5 years for bone located ES and 39% for metastatic bone ES [1,7].

It should be noted that it is described that, in most cases at diagnosis, the size tends to be larger than 20 mm in diameter, which may reflect its rapid growth [1]. In our case, the PCES was diagnosed with a diameter less than 20 mm, but also presented a rapid growth and early onset of loco-regional metastases.

The diagnosis, as mentioned previously, is made by histopathology, immunohistochemistry and cytogenetic [7,10,11]. The histopathology is characterized by small round cells with hyperchromatic nucleus and a single nucleolus [10,11]; often they are classified in the group of small blue cell tumors including neuroblastoma, alveolar rhabdomyosarcoma and lymphoblastic lymphoma. Cells typically have little cytoplasm, weakly eosinophilic and usually contains glycogen as acid Schiff (PAS) positive and round nuclei with chromatin distributed evenly and low mitotic activity [2]. Generally, 90% of ES cells express classical adhesion receptor CD99 to immunohistochemistry [7,9] having a role in leukocyte migration across the endothelium. According to the degree of neuroectodermal differentiation, it could also express neuro-specific enolase (NSE), S-100 and CD 57 vimentin positive and 20% positivity for anti-cytokeratin [10,11] antibodies. It differs from tumors of small blue cells, by their immune-histochemical characteristics, unlike lymphoblastic lymphoma that express CD99 and CD45. In the case of neuroblastoma, NSE and S-100 are expressed, but has positive neurofilament and negative vimentin; in alveolar rhabdomyosarcoma expresses CD99, but positive desmin and myogenin [10,11].

Cytogenetic is characterized by a specific chromosomal translocation involving the EWSR1 gene located on chromosome 22q12 [6,7,10]. It presents a proto-oncogene, categorized as FLI1, which expresses a protein of the same name, which promotes transcription factors, proliferation, and differentiation, which would be essential molecular pathogenesis of these tumors [3].

The differential diagnosis of this group of tumors (PCES) include BCC, keratoacanthoma, gangrenous pyoderma, Merkel cell carcinoma, small cell lymphoma, malignant melanoma, metastases of small cell lung cancer, myoepithelial carcinoma, skin metastases derived from bone Ewing's sarcoma, neuroblastoma and neuroendocrine carcinoma, lymphomas, rhabdomyosarcoma; among the most common [10].

In a review of 13 cases of PCES by Ehrig *et al.* [9], it described the cutaneous sarcomas had better survival than other types of Ewing's sarcoma. Treatment consisted of a wide excision, chemotherapy in 9 of them and radiotherapy in 6 cases who participated in the research. One patient developed gastric metastases and death at 3 years of follow-up; and the remaining patients remains disease free at the time of the study with an average of 9 years of follow-up [9]. Casuistry case of this study is too small to draw definitive conclusions, so we suggest that further studies are needed to establish the best survival proposal for the PCES. However, these findings have been corroborated by more recent studies in literature, for we find repeatedly that has a better prognosis than bone presentation [11, 12], a fact that could be explained by the smaller size at diagnosis, earlier diagnosis given its early recognition by presenting more superficial and therefore lower rate of metastasis, achieving removal of entire tumor and thus preventing future metastasis. Although world literature reinforces a better prognosis for Ewing's sarcoma skin, in our particular case, such outcome was not met, because despite being diagnosed at an early stage, the patient had an aggressive evolution, rapid and lethal. This

could be explained by our patient was an elderly, with concomitant diseases, and not a pediatric or young patient, where the evidence shows a better prognosis. Another explanation could be that our patient may have an undiagnosed immunosuppression disease and had an impaired immunity, for example because of his of diabetes, a theory that was not achieved to demonstrate due to their early demise. Another explanation could be that this tumor was a more aggressive strain, with some genetic and histological variant, that it not reached to be studied.

We must take into account the difficulty of the histological study, but has now improved considerably with the aforementioned immune-histochemical markers and could delay the correct diagnosis. We propose that the best survival described in primary cutaneous Ewing's sarcoma could be due to an earlier diagnosis because the lesion is located in an area generally visible to the patient and physician, drawing early attention. However, the correct diagnostic is not always achieved in the first instance, because of its rarity, and its low clinical suspicion, delaying the appropriate studies and stains.

Regarding treatment recommendations, a standard therapy has not yet achieved [6]. The need for complete removal of the tumor, with wide resection it is the mutual agreement [1]. It has been proposed for both, bone and skin Ewing's sarcomas, the importance of neoadjuvant chemotherapy with optional radiotherapy, being well established by Delaplace *et al*. [1,6], associated with a wide surgical margin [1,11].

Currently in patients with Ewing's sarcoma are trying to homogenize the treatments, independent of its location (both bone and extraskeletal), and their metastatic stage. The treatment lies in the combination of surgery, chemotherapy and occasionally radiation therapy, as adjuvant treatments [1, 2, 3, 9], but despite these multiple attempts survival rates still remains low (50%) at 5 years, and 25 % when it has metastasized at diagnosis for cases of bone manifestation [4, 11].

Another study found that since the association of surgical treatment to chemotherapeutic drugs significantly increased survival [14], which is consistent so described by Delaplace *et al*. This is a very important point for us, for our patient was treated just prior to his death with wide surgical excision and lymphadenectomy, without performing chemotherapy or radiation therapy, which could have improved his survival.

Progress in the treatment of ES, has improved survival from about 10% in the period before chemotherapy was introduced to about 75% today for patients with localized tumors. However, patients with metastases still fare badly, and the therapy carries short-term and long-term toxicities. Multidisciplinary care is indispensable for these patients. Molecular techniques and new imaging modalities are affecting the diagnosis and classification of patients with ES [15].

In addition to improvements in diagnosis and potentially the stratification of patients for risk, biological investigations of these gene fusions may define targets for much needed therapeutic strategies to eliminate minimal residual disease or metastatic disease [16].

We suggest that this patient should be an alert to physicians who face skin lesions growing very fast, and farther studies are needed.

CONCLUSIONS

The PCES, requires more reports in the literature to better characterize, and ideally a high clinical suspicion in a case of fast-growing tumor. It is a poorly described tumor, since it has a low frequency, and the diagnosis is often difficult due to the low clinical suspicion; but early exposure of the most superficial tumors and rapid growth should be a warning to the doctor. Because of its high morbidity and mortality and high metastatic power it should be within our list of differential diagnoses.

We propose that this disease requires a multidisciplinary confrontation of Dermatologists, supported by oncologists and surgeons. the need for a wide and complete surgical resection, associated with early onset of neoadjuvant as an essential part of the treatment of this tumor with aggressive behavior is suggested.

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Received on 28-10-2016 Accepted on 10-12-2016 Published on 29-03-2017

DOI: https://doi.org/10.12970/2310-998X.2017.05.04