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Penile primary melanoma: analysis of 6 patients treated at Brazilian national cancer institute in the last eight years

Gustavo Ruschi Bechara, Aline Barros de Santos Schwindt, Antonio Augusto Ornellas, Diogo Eugênio Abreu da Silva, Felipe Monnerat Lott, Franz Santos de Campos

Departments of Urology (GRB,AAO,DEAS,FML,FSC) and Pathology (ABSS), Brazilian National Cancer Institute, Rio de Janeiro, RJ, Brazil

ABSTRACT

Purpose: To describe our experience in treating penile melanoma in 06 patients followed at our institution.
Materials and Methods: Between 2004 and 2012 six consecutive patients with penile melanoma were treated at our Institution. Stage of the disease was classified according to the 2002 AJCC pathologic system. Melanoma in situ (TIS) was diagnosed in one patient. One patient was staged as T1b, two patients as T2b and two patients as T4b. The clinical and pathological findings were evaluated. Immunohistochemical tests were performed for Melan-A, HNB-45, S-100 and C-KIT. All histological specimens were examined by the same pathologist (ABSS). The patients with Cis, stages T1b and one patient T2b underwent only local excision. One patient T2b underwent local excision and sentinel lymph node dissection. Two patients with melanoma stage T4b underwent partial penile amputation. One of these last patients had palpable inguinal lymph nodes at diagnosis and underwent bilateral inguinal lymphadenectomy and received systemic chemotherapy (dacarbazine, 30 cycles).
Results: Mean follow-up was 36.3 months. One patient, with stage T2b, died after 12 months due to disease recurrence with bilateral inguinal involvement. The patient who underwent chemotherapy progressed with lung metastases and died after 14 months of follow up. The disease-free survival at five years was 33.3%.
Conclusion: Penile melanoma is a disease with poor prognosis in most cases. Local excision or partial penile amputation may have effective control for stages T1 and T2 lesions. Patients who have clinically proven metastases died despite surgical and adjuvant chemotherapy.

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INTRODUCTION

The first case of penile melanoma was described by Muchison in 1859 and the first report of melanoma of the urethra was made by Tirell in 1871 (1). Primary penile melanoma and in male urethra are rare malignant neoplasms that mostly affects elderly patients, from the sixth and seventh decades of life (2). There are approximately 200 cases described in the literature, representing less than 1.4% of primary carcinomas of the penis (3). Most frequently, the lesion is located on the glans (55%), followed by foreskin (28%), penile shaft (9%) and urethral meatus (8%) (4).The involvement of urinary tract mucosa

is more common in females and the explanation is the higher concentration of melanocytes in the mucocutaneous border of the vulva (5).

A problem in clinical practice is recognizing a pigmented penile lesion as a melanoma. The use of the dermatoscope may be useful in differential diagnosis with other pigmented skin lesions such as: melanosis, nevus, lentigo, and atypical pigmented macula of penis, however the diagnosis must be made by biopsy of the lesion. Indeed, one of the major mimickers of mucosal melanoma, and thus of penile melanomas, is melanosis. Clinically, despite its benign behavior, melanosis can, at times, share features with malignant melanoma as asymmetry, irregular borders, multifocality, variegated pigmentary patterns and large size. Due to late diagnosis and lack of well established treatment protocols, the prognosis is generally poor. However, although it is an aggressive disease, it is possible to maximize cure with treatment in its early stages.

Given the rarity of the disease, we report our experience with the treatment of six patients with penile melanoma between 2004 and 2012.

MATERIALS AND METHODS

We reviewed, after approval by the INCA Ethical Committee with the number 38/05, the charts of six patients who were consecutively admitted to Brazilian National Cancer Institute to treat penile melanoma between 2004 and 2012. After detailed anamnesis, physical examination was performed with careful palpation of the primary lesion and the inguinal region, seeking palpable lymph nodes. Following, we performed a biopsy of the lesion. A case of melanoma in the penile glans is shown in Figure-1.

All slides were reviewed by a single pathologist (ABSS). All tumors were evaluated for major prognostic factors. To determine the real extent and dimension of the injury, the analysis included the depth (Breslow) and size of the lesion, the presence or absence of necrosis, ulceration and satellite nodules. We also analyzed the number of mitoses per field, presence or absence of associated in situ melanoma (Tis) and characteristics of resection (R0, complete or R1 when the margins were positive).

Regression was observed in associated area of lesion "in situ". Figures of mitoses, ulceration, and vascular or perineural invasion were not observed. In the second case, the slides showed ulcerated tissue fragments, and necrotic tumor emboli that populated vessels and corpus cavernosum, constituting sometimes, metastatic nodules. Areas of regression were observed. Mitoses were not found and the thickness of the lesion and stage could not be assessed. Viral cytopathic changes consistent with HPV were observed even in non-neoplastic skin.

In tumors occurring in the mucosa, one originated in the glans, and the other into the urethral orifice. The glans had a nodular type melanoma measuring 2 mm thick. It had no mitoses, vascular invasion or regression. But there was perineural invasion and foci of ulceration graded as pT1b. In the second case the injury that began in the mucosa of the urinary meatus, in an average of 7 mm, was

Figure 1 - Pigmented, exophytic and irregular lesion with poorly defined borders, located in and around the glans meatus, measuring approximately 3.0 cm.

An immunohistochemical study from the fragments obtained was performed for Melan-A, HNB 45, c-kit (Figure-2) and S-100. In patient with Tis we were unable to perform immunohistochemical examination due to shortage of material to be examined. In the other 5 cases, the examination was done for both Melan-A and S100. The HMB45 was done in 2 cases. The c-kit (CD117) was made in 5 cases and marking was performed on the desmoplastic melanoma.

The preoperative staging included chest radiography and abdomen and pelvis CT. The tumor staging was based on the 2002 American Joint Committee on Cancer (AJCC) to classify melanoma (Table-1). In this system, pathological tumor stage is mainly based on the evaluation of lesion depth (Breslow) and anatomic level of invasion (Clark). Our approach for the treatment of melanoma of penis is detailed in Figure-3.

RESULTS

Patient ages ranged from 14 to 78 years with a median age of 72 years. Surgical treatment varied with histopathological staging. Of the 6 patients, 2 (33.3%) had lesions on the glans, 2 (33.3%) in the foreskin, one (16.7%) in the body of the penis and one (16.7%) in the meatus of the urethra (Table-1).

One patient had Cis, 1 was staged as T1b, 2 staged as T2b and 2 as T4b. Patients with melanoma stage T2 or less underwent local excision with adequate safety margin of approximately 2 cm, although we believe that 1 cm is enough. The most important thing is the absence of tumor cells in the material sent for freezing. If the margins are positive, they are extended and a new material is sent to be analyzed. The consensus is surgical margin of 1 cm for lesions up to 1 mm thick and surgical margins of 2 cm for lesions measuring more than 2 mm. Five patients had not palpable inguinal lymph nodes at diagnosis. Three of the five patients were observed without additional therapy. One patient with stage T2b underwent bilateral sentinel lymph node biopsy, which was negative. Other patient with stage T2b died after 12 months with recurrence of disease associated with bilateral inguinal involvement. One patient with stage T1b died three months after surgery from causes unrelated to the disease (Table-1). Both patients with stage T4b melanoma underwent partial

Figure 2 - Slides of malignant melanoma of the penis: A) Malignant melanoma showing spindle cell area, containing atypical melanocytes. (HE - 200x). B) Same case immunostained for HMB45 (400x). C) Immunoreativity for Melan - A (400x), a product of gene MART 1. D) c-KIT (400x), product of c-kit gene expression. It is a transmembrane protein.

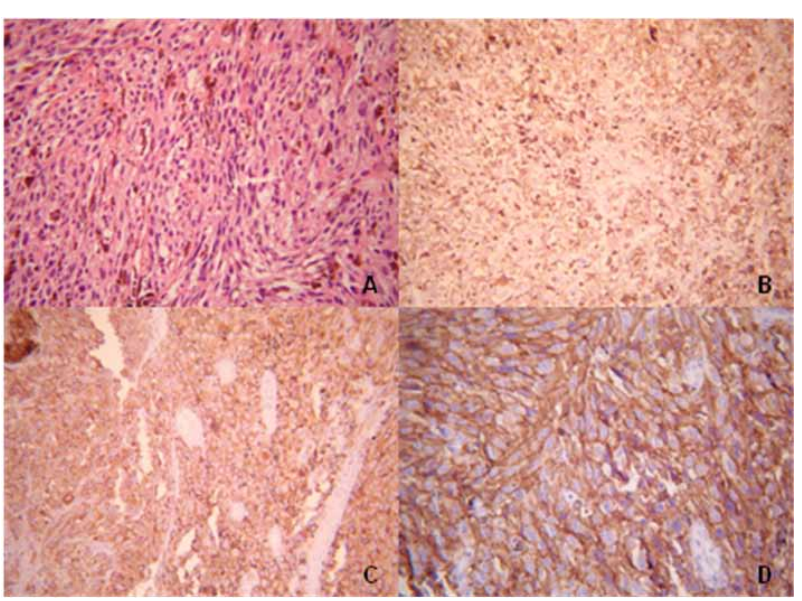

Table 1 - Clinical and pathologic characteristics of the tumors studied.

Patients	1	2	3	4	5	6
Date of surgery	2004	2005	2005	2006	2007	2012
Age (years)	14	64	73	75	71	78
Site of tumor	Glans	Foreskin	Shaft	Foreskin	Glans	Urethral Meatus
Pathologic Stage (AJCC 2002)	T in situ	T2bN0M0	T2bNXM0	T4bN3M1	T1bNxM0	T4NxM0
Palpable Lymph nodes	Negative	Negative	Negative	Positive	Negative	Negative
Breslow (mm)	In situ	1.9 mm	1.5 mm	10 mm	0.2 mm	7 mm
Primary Therapy	Local Excision	Local Excision + Sentinel Lymph node Dissection	Local Excision	Partial Amputation + Bilateral Inguinal Lymph node Dissection	Local Excision	Partial Amputation
Recurrence	No	No	Yes	Yes	No	No
Adjuvant Therapy	No	No	No	Dacarbazine (30 cycles)	No	No
Follow-up (months)	96	84	12 (Death)	14 (Death)	3 (Death)	9

penile amputation. Only one patient had palpable inguinal lymph nodes at diagnosis, and then underwent bilateral inguinal lymphadenectomy. The histopathological finding revealed lymph node metastases in one of seven lymph nodes on the right and in three of eleven lymph nodes on the left. This patient was then referred to the oncology service, where he underwent chemotherapy with dacarbazine (30 cycles). The patient developed lung metastasis despite systemic chemotherapy and died after 14 months of follow-up. In the other case, we opted for not performing inguinal lymphadenectomy due to old age and associated co-morbidities (Table-1). Of the 6 tumors evaluated, 3 originated in the skin, one occupying the body of the penis, and 2 the foreskin. The tumor in the body of the penis was in the vertical growth phase, had a thickness of 10 mm and pT4bN3M1 stage, contained satellite nodules, ulceration and regression. Mitotic figures reached the highest number (17/mm^2) and tumor infiltration was observed in the dermis and in the corpora cavernosa, making neoplastic emboli. Inguinal lymph node metastases were found bilaterally (Table-2).

The first case, with tumor occurring in the foreskin, had a tumor desmoplastic (pT2b), extending to the dermis in an average of 1.9 mm. The tumoral pigmented melanocytes were mixed with thin beam spindle setting the standard desmoplastic.

Figure 3 - An algorithm showing our treatment for patients with melanoma of penis.

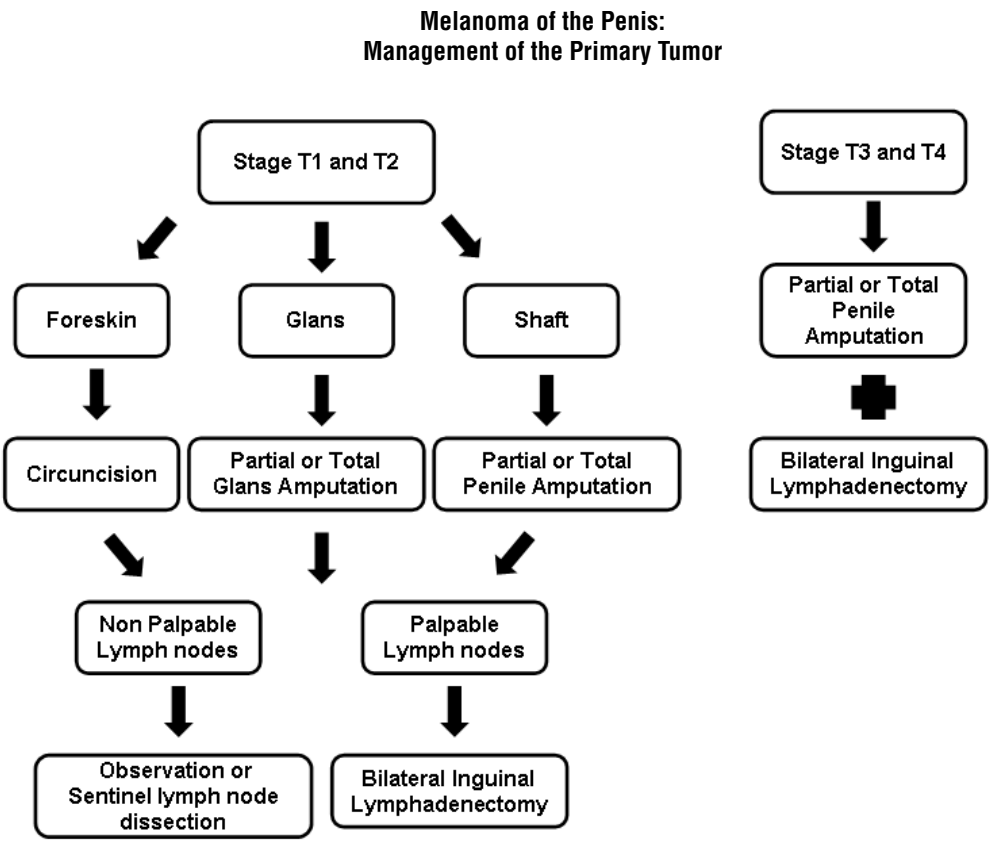

Table 2 - Histological characteristics of the tumors.

Pts.	Invasion	Ulcers	Necrosis	Satellites nodules	Regression	Inflammation	Mitosis (mm^3)	Tis	Associated Lesion
1	Dermis	present	present	present	absent	mild	5	absent	Lupus
2	in situ	absent	absent	absent	present	mild	absent	absent	absent
3	dermis / epithelium	absent	absent	absent	present	mild	absent	present	absent
4	dermis / epithelium / vascular / sebaceous	present	present	absent	present	absent	17	present	absent
5	dermis/ epithelium	present	present	absent	present	moderate	absent	present	HPV
6	dermis	present	absent	absent	absent	absent	absent	absent	absent

staged as pT4 and had angiolymphatic invasion. The tumor had 5 mitoses / mm^2, ulceration and was in the vertical growth phase, with peripheral radial growth area represented by melanoma "in situ". The regression did not follow the development of the lesion. Lupus erythematosus was observed in non--tumor skin area.

The predominant histological pattern was that of melanocytic cells rounded and large, with cytoplasm ranging from clear to eosinophilic, containing nuclei presenting gross atypia and evident nucleoli. Multinucleated giant cells were seen in smaller numbers. Melanocytes were isolated from tumor nests or neoplastic mass of cohesiveness variable. In case 5, whose tumor was nodular, the pattern of rounded melanocyte was mixed with elongated fusiform cells, similar to sarcoma. The dermis exhibited varying degrees of stromatous reaction, vascular proliferation and inflammatory infiltrate.

In immunohistochemical examination (Table-3) the staining was strongly positive in 5 cases, both for Melan-A, and for the S100, but the amount of labeled cells was above 50% in 3 cases and 40% in the two other cases. In the HMB45 done in 2 cases at diagnosis, intensity was strongly positive, with 30 and 20% of labeled cells in 2 cases respectively. The c-kit (CD117) and marking in the desmoplastic melanoma was strong in 30% of cells balloon-shaped and weak in fusiform cells, over 50% marking in two distinct types of cells. For cases of melanoma in vertical growth, staining was strong and over 50% of cells, being negative in case 5, the nodular (pT1b).

In our series of penile melanoma patients, disease-free survival was 33.3% at five years. Recurrence occurred in 2 patients after 12 and 14 months respectively, with mean follow-up period of 36.3 months.

DISCUSSION

Penile melanoma is a rare disease that affects mainly elderly patients, from the sixth decade of life, unlike cutaneous melanoma, whose incidence is higher in young patients (40-50 years) (2). One of our patients, however, with 14 years of age showed an in situ (Tis) melanoma in the glans, successfully treated by local excision and remained disease-free after a follow-up of 96 months after surgery.

Patients are usually asymptomatic, but in advanced stages, may have dysuria, obstructive symptoms, hematuria, urethral discharge and more rarely urinary fistula (6).

Presentation ranges from papule or plaque staining bluish-black or reddish brown with bleeding ulcer. These lesions are usually benign completely indistinguishable clinically from primary penile melanoma (7). Dermoscopy may prove useful for the differential diagnosis between mucosal melanosis, and other mimickers, and early melanoma. However, its potential role has been limited so

Table 3 - Immunohistochemical characteristics of tumors.

Patients	Melan-A	HNB 45	S 100	C-kit
1	+ 50% Strong	x	x	positive
2	+ 50% Strong	x	x	positive
3	+ 50% Strong	x	x	positive
4	+ 40% Strong	x	x	positive
5	+ 40% Strong	positive	positive	negative
6	+ 50% Strong	positive	positive	positive

far because little is known about the dermoscopic features of penile melanoma (8).

Diagnosis is made by biopsy of the lesion. Histopathological examination demonstrates increased activity of atypical junctional cells and detachment of pigmented cells in the dermis (8,9).

Microscopic criteria as asymmetry, cell nests confluence, junctional activity, atypia and necrosis of melanocytes are important for a conclusive diagnosis. In difficult cases we have used immunohistochemistry. Although that is not necessary in cases of well- differentiated tumors, it is indispensable in poorly differentiated tumors. The more specific markers for melanoma are melan-A (MART-1), HMB 45 and S-100 protein. Besides these, information about the aberrations of c-Kit gene in acral melanomas in mucosa or in areas of permanent sun exposure, are targeting therapeutic research, making these aberrations an important marker (10-15). Immunohistochemistry performed in five cases for c-kit was positive in more than 50% of cells with good intensity in 4 cases and negative in one (case 5 with tumor in glans, pT1b).

Thickness of the lesion, presence of ulceration, and mitotic figures are considered major predictors of survival. The presence of metastases to lymph nodes and metastatic nests satellites is also valued. This consensus applies to tumors of the skin, and consequently, of the penis, which is covered by skin (16). The thickness of the primary tumor is a predictor of recurrence, especially if associated with ulceration and high mitotic rate (17). Many melanomas begin with the radial growth phase through the stages "in situ" and microinvasive (18). In the vertical phase, progression occurs through its expansion into the dermis where the measured thickness will vary with the histological type. For example, nodular melanoma exhibits the largest thickness among the other types (19). The average thickness is increased in cases of fatal melanomas (19). Absence of ulceration is proportional to the increased specific survival rate and disease free survival at 5 years (20). As we have seen, the ulceration was present in 4 cases we evaluated. Two of them reached great depths (7 and 10 mm) and pT4 stage. In a third case, the thickness of the lesion could not be measured, probably because of severe necrosis, associated with ulceration that became the injury brittle, leading to easy fragmentation of the material.

Rate of mitosis is used to stage melanomas and their presence outweighs prognosis necrosis. But the absence of mitosis does not invalidate the diagnosis of malignancy (16). Vascular invasion is another independent factor related to survival and disease-free survival. Presence of intralymphatic neoplastic cells was criterion for evaluation of metastasis to the category N (16). Vascular invasion was present in both melanomas on the skin and on the mucosa, infiltrating vessels and corpus cavernosum. Microscopic metastases found on the reticular dermis or fat, in the same section from the tumor, distant more than 0.05 mm from the lesion, are called satellites (21). Tumor nodule with these characteristics was observed in case of melanoma in the penis shaft (pT4N3M1). The behavior of the tumor in the phase of regression has been widely discussed as an indicator of disease progression. Sentinel lymph node metastasis occurs in melanomas with vertical growth and regression, but does not occur in cases of radial growth with regression (22). T lymphocytes responsible for autoimmune reaction and mechanisms of programmed cell death are believed to be involved in the mechanism of regression. But it seems that instead of controlling the growth of the tumor, the autoimmune reaction accelerates this growth (23). In this case, the regression would not be the result of immune toxicity, but the rapid differentiation of cells, contributing to a more aggressive behavior (24). In place of regression are found lymphocytes and phagocytic cells loaded with melanin angiolymphatic vascular reaction and delayed fibrotic scarring permeated with neoplastic cells isolated (25). The lymphocytic infiltrate was present in almost all our cases, both around the injury and / or in the middle of it, remembering their relationship with immune regression. The regression was present in over half of our cases, but only in case 2 (pT4N3M1) was accompanied by metastases to lymph nodes.

Van Geel et al. reported 19 patients diagnosed and treated at an interval of 25 years. Early diagnosis was critical, since the prognosis is poor, with an overall survival rate at 2 and 5 years of 63% and 31% respectively. Most patients were

diagnosed too late, which reduced the cure rates of disease. All patients with lymph node involvement or distant metastases at diagnosis died within two years despite surgical treatment. Tumor greater than 15 mm, presence of ulceration and tumor depth greater than 3.5 mm had a worse prognosis (26).

Chemotherapy is indicated for disseminated melanoma. The combination chemotherapy consisting of six cycles of DTIC, BCNU, cisplatin and tamoxifen presents the best result. The response rate to therapy varies between 15% and 45% (27).

Given the rarity of the disease, the best treatment for penile melanoma remains uncertain. Stillwell et al. from the Mayo Clinic reported 11 consecutive patients treated over a period of 66 years. All patients underwent conservative treatment, including the amputation of the glans in 6 patients, local excision in 3 and partial penile amputation in 2 (3). They believe that conservative surgery such as local excision or partial penile amputation with appropriate safety margin (3-5 cm), can be performed in superficial lesions (less than 1.5 mm) or associated with superficial bilateral inguinal lymphadenectomy in deeper lesions (greater to 1.5 mm), thus being suitable for melanomas stage T1 or T2 (27-29). However, lack further evidence for defining the optimal surgical margin for lesions with a thickness between 1 and 2 mm, and it is the current trend to practice banks of 2 cm. In addition there are very few studies dealing with more severe injuries, thicker than 4 mm, for example. Melanoma in situ is also poorly evaluated in these aspects and recommendations are very variable ranging from 0.5 to 1 cm of surgical margins. In our study, all patients were treated conservatively, including glans amputation in 2, local excision in 2 and distal third penile amputation in 2. Subsequently 4 of the 6 patients (66%) were rendered disease-free.

All patients who persist with palpable inguinal lymph nodes after antibiotic use shall be submitted to bilateral superficial inguinal lymphadenectomy. The treatment in relation to patients without palpable lymph nodes is controversial. Although the overall incidence of inguinal lymph node metastases varies between 43% and 62%, the incidence of metastatic disease in patients with early-stage disease is significantly small. Thus, a large proportion of patients clinically negative for the disease can not benefit from prophylactic bilateral inguinal lymphadenectomy. Other authors have reported that sentinel lymphadenectomy avoids potential morbidity related to inguinal lymph node dissection and allows accurate staging for further treatment and assessment of prognosis (27,30). The inguinal lymphadenectomy is clearly indicated in patients with stage T3 or T4. Patients with palpable lymph nodes that do not resolve after antibiotic treatment should undergo inguinal lymph node dissection. Chemotherapy and radiation treatments are only palliative or adjuvant. (31).

CONCLUSIONS

Penile melanoma is an uncommon disease, in most cases with poor prognosis due to the late diagnosis and lack of treatment protocols well established. Local excision or partial penile amputation, with appropriate safety margin, can be effective in the control of stages T1 and T2 penile melanomas. Yet patients who had clinically proven metastases died despite surgical procedures and chemotherapy. Although it is an aggressive disease is likely to be cured when in the early stages, making necessary a close cooperation between urologists and dermatologists to achieve this goal. The treatment of patients without palpable lymph nodes is controversial, however, considering the aggressiveness of the disease and early metastasis, prophylactic inguinal lymphadenectomy may be considered in selected patients.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Antonio Augusto Ornellas, MD
Department of Urology
Instituto Nacional de Câncer
Praça da Cruz Vermelha, 23
Rio de Janeiro, RJ, 20230-130, Brazil
E-mail: ornellasa@hotmail.com