Merkel cell carcinoma – a clinical case report

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Abstract

The authors present the clinical case of a 68 year-old woman admitted to an Internal Medicine ward with diagnosis of pulmonary embolism. During the admission process, the results of the histopathological analysis of a previously biopsied inguinal lymph node cluster were obtained, revealing metastases suggestive of Merkel Cell Carcinoma (MCC). After a thorough examination of the skin, the primary tumor was located, and was of unusual localization and characteristics.

The rare incidence of this neoplasm, and its unusual clinical presentation, justify reporting this case.

Key words: neuroendocrine carcinoma, skin tumor, Merkel cells, venous thromboembolism.

Introduction

Merkel cell (Cutaneous neuroendocrine) carcinomas, also known as MCC, are rare neoplasm, usually observed in the elderly population. Their diagnosis is based on histology and confirmed by immune-histochemical studies. Main characteristics are their high recurrence rates and metastases, and also their poor prognostics.

Cutaneous neuroendocrine carcinomas were originally classified under the name of trabecular carcinomas, by Toker, in 1972, and are now commonly known as MCC.[1-5] Most authors assume that MCC originates from the Merkel cells located in the basal epidermis and dermo-epidermal junction, and it is closely associated with myelinated nerve fibers. [1,2] The histogenesis of MCC has yet to be determined. Three different hypotheses are considered: epithelial origin with neuroendocrine differentiation; origin in a pluripotential epidermal stem cell; or origin in a dermal neuroendocrine cell.[1]

Venous thromboembolism (VTE) is a common complication in oncological patients, and is an important cause of morbidity and mortality.[6]

There are two hypotheses for the association between VTE and cancer: cancer patients have a higher risk of thrombotic events, and idiopathic VTE may be the first sign of a hidden malignancy.[6]

Clinical Case

A female patient, aged 68 years, Caucasian, born and resident in Coimbra, retired, who arrived at the Emergency Unit of the HUC on August 16th, 2004 due to left thoracalgia with pleural characteristics and dyspnea, 12-hour evolution, and pain and edema of the right leg. The patient had recently undergone biopsy for a tumefaction of the right inguinal region, with onset around five months previously and gradual, painless growth. Patient reported edema of the right leg, which gradually worsened in the last days.

Personal history included high blood pressure, depression and psoriasis. In terms of drug use, she reported taking amlodipine, atenolol, valsartan, indapamide, tianeptine and diazepam. She did not smoke or drink. The family history was not relevant.

On objective examination at the Emergency Unit, patient was conscious, collaborative and oriented. She was apyretic, with flushed, moist skin and mucosa. In the lung auscultation, the vesicular murmur was reduced in the left lung base. The heart auscultation was rhythmic. The abdomen was smooth and depressible, without palpable masses or organomegalies. Blood pressure was 120/70 mmHg. There were no palpable adenopathies in the cervical, axillary and inguinal lymph node chains. Patient had marked edema on the right leg, without signs of inflammation,

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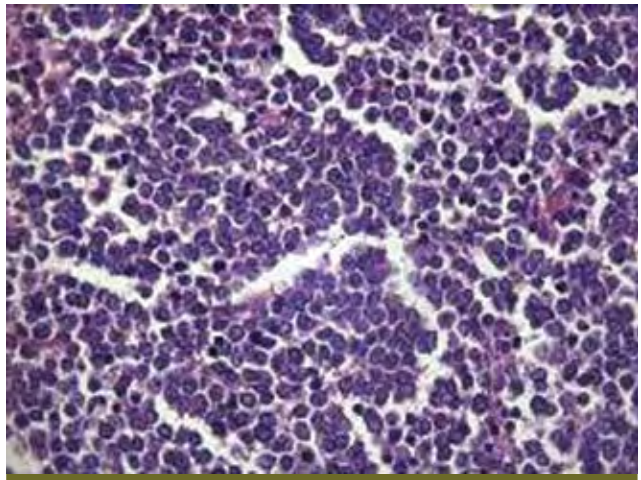
and with negative Godet signal, causing functional inability to walk.

The laboratory data showed C-Reactive Protein of 9 mg/dL (normal value < 0.5), lactate dehydrogenase of 481 U/L (normal value 135-225) and fibrin degradation products of 5.8 µ/ml (normal value < 0.6). Arterial gasometry revealed hypoxemia with pO2 of 63 mmHg. Chest radiography showed signs of a possible left pleural effusion. For ventilation-perfusion lung scintigram revealed marked scintigraphy perfusion defects in the lower left lobe and basal and upper segments of the lower right lobe, indicating a high probability of PTE.

The patient was admitted to the Internal Medicine ward with a diagnosis of PTE, probably originating from deep venous thrombosis of the right leg, for further etiological and therapeutic investigation. During the admission process, the histological result was obtained for the adenopathy cluster previously biopsied. Metastasis was found from a neuroendocrine carcinoma, with extensive layers of rounded cells with monotonous nuclei and thin, clotted chromatin, with significant mitotic activity and positive cytokeratin 20 (CK20) expression in a cytoplasmatic "blurring", and neurospecific enolase suggestive of cutaneous Merkel carcinoma.

As the location of the primary tumor was unknown after the initial clinical evaluations and supplementary examinations, exhaustive and repeated skin tests were performed, which located, on palpation, a small, painless, migratory, hard, dermal, nodular lesion of around 2 cm in diameter in the right buttock, causing a slightly mauves erythema on the surface, which was difficult to see and evaluate. This lesion had evolved over 6 months, as it was not given due attention by the patient, and was biopsied. Histological study of this lesion showed a multi-nodular infiltrate of cohesive cells and scarce cytoplasm, hyperchromatic nuclei and fine, granular chromatin. Immune-histochemical study revealed positivity of the neoplastic cells for CK20 (cytoplasmatic blurring type) and for neurospecific enolase (NSE) confirming the diagnosis of primary cutaneous Merkel carcinoma *(Figs. 1, 2 and 3)*.

Of the remaining tests carried out, Doppler echography of the right leg was highlighted, which showed a solid, hypoechogenic, irregular mass involving the right iliac vessels, resulting in obstruction of venous flow. Although no organized clots were evident in the veins of the right leg, these veins presented ectasia and



Histological characteristics of cutaneous MCC (H&C). Cohesive cell infiltrate of scarce cytoplasm and hyperchromatic nuclei with granular chromatin.

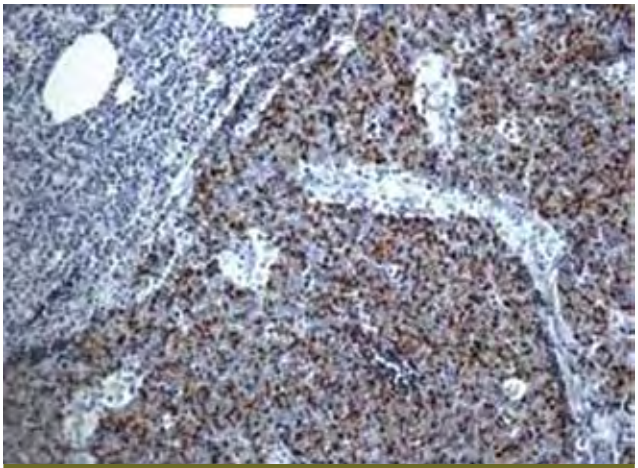
FIG. 1

were filled with blood described as very thick. Computed tomography (CT) scan of the chest, abdomen and pelvis revealed an adenopathic cluster in the right pelvis measuring 11 x 5 cm, which included the iliac artery, though without distorting or compressing it, and a small layer of left pleural effusion.

The treatment initiated in the Medicine Service included enoxaparin, warfarin and oxygen therapy, as well as the usual outpatient therapy.

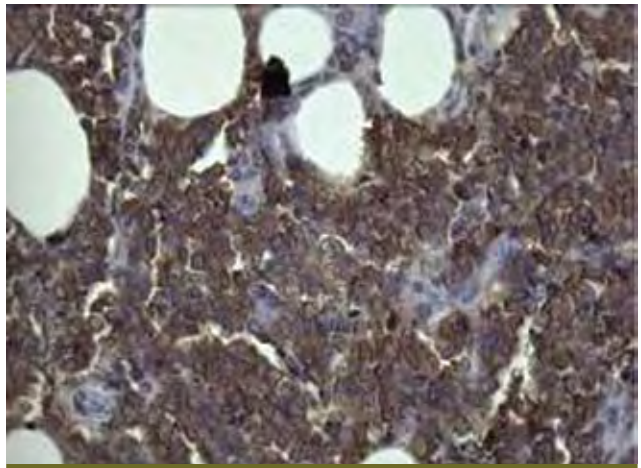
The patient was transferred to the Dermatology Service on July 9th, 2004, where she began polychemotherapy. Five cycles of CAVP (cyclophosphamide, doxorubicin, vincristine and prednisolone) were administered, during which time enoxaparin was combined, replacing the warfarin. Partial reduction of the pain and edema in the right leg was observed, and the patient was able to walk. Following the cytostatic therapy, warfarin was reintroduced, replacing the enoxaparin. No recurrence of thromboembolism was registered.

The patient was observed in the Dermatology Center, with no manifestations of local regression or lymph node metastasis. A CT scan, performed four months after onset, did not show any expansive processes in the pelvic cavity or adenopathies in the iliac chains (*Fig. 4*). After 10 months, the patient complained of pain in the left iliac fossa, with a palpable mass in this region and a hard, poorly-defined hypodermal



Immunohistological characteristics of cutaneous MCC. Positive results for CK20 in "cytoplasmatic blurring".

FIG. 2



Immunohistological characteristics of cutaneous MCC tumor. Positivity for neurospecific enolase.

FIG. 3

nodule of about 4 cm, located on the surface of the right thigh. CT of the chest, abdomen and pelvis revealed three expansive lesions, one of 7 cm diameter in the left iliac fossa, located within the iliac vessels, one of 4cm in the left inguinal region, and one of 2 cm in the suprapubic region. Based on these findings, it was decided to reinitiate chemotherapy with cisplatin and etoposide. As no clinical improvement was observed, the cytostatic therapy was suspended, and the patient died after three months.

Discussion

The annual incidence of MCC is 0.23/100,000 inhabitants among the White population, a figure which is far higher than among the Black population, which is 0.01/100,000 inhabitants.[5] The ratio of males to females is 1.4/1.0.[4] Most cases occur between the seventh and eighth decades of life,[1] with 5% of the cases occurring in subjects aged 50 years or under.[5]

The etiology of MCC remains unknown. It is argued that UV radiation may lead to the development of this type of tumor.[1,5] This neoplasm increases in frequency and aggressiveness after immunosuppression, organ transplant, and B-cell neoplasm.[1,4,5] Patients with psoriasis treated with PUVA have a greater chance of developing MCC.[7] A significant proportion of MCC is associated with malignant epithelial neoplasias.[1,4,5] In the patient in question, no association was observed with any of the above clinical entities, and there was no prior treatment with PUVA.

MCC is usually observed as a non-ulcerated, migratory, painless, hard, dermal nodule, with slightly erythematous coloration, a deep mauvish color, and rapid growth, of 0.5 to 5 cm diameter.[1,2,3,4,5] The edges of the tumor are diffuse and the underlying skin is generally intact.[1,4] In 47% of cases, the tumor is located on the head and neck, in 40% it is on the hands and feet, in 8% it is on the trunk, and in 5% of cases, the primary location is unknown.[5] The onset and location of the primary tumor described in this clinical case report were atypical.

In histological terms, MCC is a tumor located in the dermis, sometimes extending to the subcutaneous tissue and muscle.[1,2] The epidermis is usually saved, and in rare cases, Pagetoid growth of tumor cells occurs.[1] This consists of small, round, uniform cells, with a thin cytoplasmatic ring and nucleolus with finely scattered chromatin.[1,2,3,5] There are 3 subtypes of MCC: "trabecular", "intermediate cell" and "small cell", and the association of characteristics of the various subtypes is common.[1] The diagnosis of MCC should be confirmed by immunohistological methods.[2,5] Like Merkel cells, MCCs express epithelial and neuroendocrine antigens.[1,2] The cytokeratins 8, 18, 19 and 20 antibodies, similar to those which act against neurospecific enolase, are particularly useful for the immunohistological diagnosis.[1,5] The chromogranin A expression is widely variable, and positivity for S-100 has been described in some situations. Tests for vimentin and the leukocyte common antigen are

consistently negative.[1,2,5] In the case presented, the positivity for CK20 and neurospecific enolase confirmed the diagnosis.

The staging system used for MCC is based on the clinical presentation. 67% of the cases were in stage I (primary tumor located), 25% in stage II (lymph node metastasis present) and 8% in stage III (distant metastasis present).[8] The patient in question was in stage II.

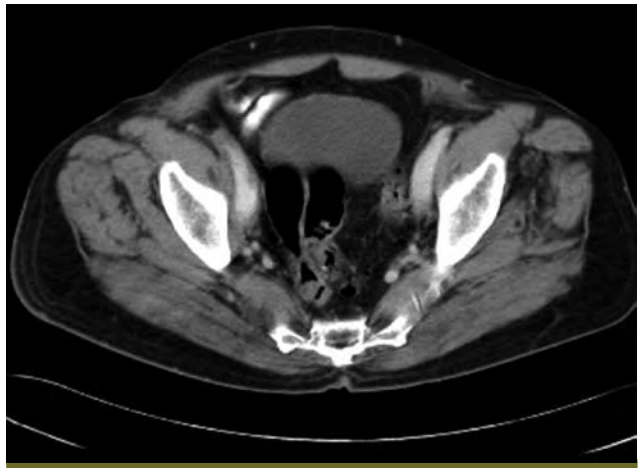
There is no standard treatment for MCC.[1,2,4] Surgical intervention includes local or wide local excision with lymph node dissection (68%), radical resection with lymph node dissection (22%), and amputation (4%). Adjuvant treatment (51%) with radiotherapy or chemotherapy, while not influencing the survival rate, reduces the recurrence rate.[8] Chemotherapy is particularly useful in patients with metastatic MCC. [1,3,5] Cyclophosphamide, doxorubicin and vincristine or etoposide and cisplatin are the most frequently used regimes.[4,5]

Unfavorable prognostic factors for MCC are: age over 65 years, male, tumor more than 2 cm, tumor located in the trunk, lymph node disease or located distant from the presentation, and duration of the disease before presentation of less than three months.[2,3,5,9] Lymph node disease on presentation and age over 65 years were factors which were present in the clinical case described.

Global survival rates are 88% in the first year, 72% at 2 years, 55% at 3 years, and 30% to 64% at 5 years.[1] During the course of the disease, 25% of the tumors reoccur locally, 52% develop lymph node metastasis, and 34% develop distant metastasis. [5] The average reoccurrence interval is 8 months, [3] with an average of 10.6 months. [8] In the patient described in the case report, the disease reoccurred at the end of 10 months.

The clinical presentation of the MCC described in this case report includes a PTE. The causes of thrombosis are blood stasis, changes in blood composition, and changes to vessel walls (Virchow's triad). [10]

There are various pathogenic mechanisms of venous thrombosis in the presence of neoplasm.[10] Thrombocytosis and increased levels of factor VIII, fibrinogen and thrombin may be present. The tumor may compress adjacent vessels, resulting in blood stasis, or invade and damage the vascular endothelium, activating the coagulation cascade.[10] Additionally, there are extrinsic factors which can lead to a state



Pelvic CT after 4 months.
No expansive processes or adenopathies in the pelvic cavity.

FIG. 4

of hypercoagulability, such as surgery, chemotherapy, and the placement of a central venous catheter. [6] The risk factors related to oncological patients are age, immobilization, obesity, thrombophilia, nephrotic syndrome and heart failure. [6,10] The tumors most frequently associated with thrombosis are tumors of the ovaries, pancreas, and central nervous system. [6] Doppler analysis performed on this patient showed compression with vein ectasia in the right leg, and although no clots were observed, the veins were described as filled with very thick blood. The conditioned edema, while associated with functional impotence, did not result in total immobility.

Anti-coagulation treatment is the preferred therapy for VTE, with a minimum duration of 12 months. In clinical practice, the association of neoplasia with VTE presents various clinical problems, in particular, a higher recurrence rate of the thromboembolism.[10] Anti-coagulation therapy was administered to the patient, and no recurrence of thromboembolism was observed.

In about 10% of patients with idiopathic VTE, there is an underlying neoplasia.[11] Clinical history, physical examination, laboratory analysis and chest radiography are recommended for patients with idiopathic VTE disease.[10]

VTE is the second most common cause of mortality in patients with cancer,[11] and around one in seven of patients hospitalized for this cause die from PTE.[6]

This case report describes several important and relevant situations in Internal Medicine. In addition to the rarity of the diagnosis, the issue of metastasis of unknown origin should also be considered, it being possible, through a thorough physical examination, to locate the primary tumor, confirm the diagnosis, and provide guidance as to the most appropriate therapy. The interest in the occurrence of venous thromboembolism and its association with malignant neoplasia, as well as the borderline between vascular compression (both venous and lymphatic, of the lower limbs) and deep venous thrombosis, in the context of PTE and cancer, are aspects to be considered. ■

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