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Cutaneous Metastasis of Neuroendocrine Carcinoma with Unknown Primary Site: Case Report and Review of the Literature

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Key Words
Neuroendocrine carcinoma · Neuroendocrine tumor · Metastasis · Skin metastasis

Abstract
We report a new case of neuroendocrine carcinoma for which it was not possible to find the primary site until now. The recent medical literature about skin metastasis of neuroendocrine carcinoma (neuroendocrine tumor) is discussed.

Introduction

Neuroendocrine tumors (NETs) constitute a heterogeneous group of neoplasia, gathered together because of their common features: tumors capable of secreting hormones, neurotransmitters, neuromodulators and neuropeptides. Neuroendocrine cells, supposedly precursors of this group of neoplasia, are found in all solid organs, skin and mucosae; therefore, NETs may originate in several locations [1–3].

Their incidence varies in different studies. Data from the US and Europe indicate an approximate incidence rate of 1–2 new cases/100,000 inhabitants per year. This represents about 0.5% of all malignancies. Some articles indicate that, although rare, NETs are presenting a discreet and progressive rise in their incidence [4].

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The gastrointestinal tract is the most common primary site (62%), where appendix (27%) and the small intestine (15%) are the most prevailing, followed by the lungs (23%). It is relevant to highlight that up to 12% of the patients present metastases from an unknown primary site [4].

Within the spectrum of NETs, on the one side, well-differentiated NETs can be found (formerly called carcinoid tumors), usually with a painless clinical course, besides being curable by simple resection when viable. On the other side of the spectrum, there are poorly differentiated neuroendocrine carcinomas (NECs), of a more aggressive clinical course, producing metastases with greater frequency and, usually, requiring isolated or adjuvant chemotherapy [1, 2]. Cutaneous manifestations from NETs are not uncommon, especially those exhibiting carcinoid syndrome. Flushing is the most common manifestation, present in all secretory tumors. Cutaneous metastases, however, are rare [3, 5].

We present the case of a patient with a diagnosis of NEC of undetermined primary site, diagnosed with lymph node metastasis and cutaneous lesions.

Case Report

A 65-year-old man with arterial hypertension was diagnosed 2 years before with NEC based on histopathological examination of a swollen lymph node in the right inguinal region. The patient was scanned with CT and scintigraphy; however, the site of the neoplasia was not identified. Nevertheless, 6 months ago, chemotherapy treatment was initiated with a combined scheme of carboplatin and etoposide.

Three months ago the patient noted nodular lesions visible on the right lower limb with progressive growth that led to the request of a consultation by a dermatologic peer.

At clinical examination, the lesions were more palpable than visible. There was no overlying erythema. They were restricted to the right thigh, in a linear trajectory, and the right buttock (fig. 1, fig. 2, fig. 3). The lesions were painless at touch, had a hardened consistency, measured up to 1.5 cm and were not adhered to deeper planes.

An excisional biopsy of one of the skin lesions was performed. Histopathological examination showed a nodule occupying the medium/deep reticular dermis and hypodermis, with expansive growth, comprising monomorphic cells with poorly defined cytoplasmic borders, round nucleus, and fine granular chromatin, delimited by delicate septa of connective tissue (fig. 4, fig. 5). Numerous figures of mitoses were noted. Immunohistochemistry showed focal positivity in paranuclear dot for CK20 (fig. 6), positivity for chromogranin (fig. 7) and synaptophysin and a cell proliferation index evaluated by Ki67 of about 60% (fig. 8). These findings were interpreted as compatible with cutaneous NEC metastasis.

The case was considered by the clinical oncologist as loss of response to treatment and progression of disease. Therefore, a chemotherapy rescue scheme was initiated with irinotecan. The patient is being followed up by both specialties.

Discussion

Carcinomas with unknown primary site represent about 2.3–4.2% of all malignant neoplasia cases (being seventh or eighth in frequency, depending on the casuistry). They seem to affect men more frequently, with onset in the fifth or sixth decade of life, being the fourth cause of death in both genders. Of these, 50% are at least moderately differentiated adeno-

carcinomas. Up to 30% are poorly differentiated, and the NETs of unknown primary site are included in this group [6].

The detection of the primary site in metastatic NET is a challenge. The approach includes endoscopy and imaging (tomography and scintigraphy). Recently, evidences indicate benefits by using endoscopic ultrasound and PET CT [7].

As a group, NETs produce metastases in 30% of cases, and among these a greater portion is attributed to NEC. The metastatic disease signals a worse prognosis. Other worse prognostic factors identified at histopathological examination are vascular and lymphatic invasion, a high grade of cell atypia, an increased nucleus/cytoplasm ratio, the presence and extension of necrosis, besides an increased mitotic index [2, 8]. The cell proliferation index analyzed by immunohistochemistry (Ki67) contributes to this assessment. Poorly differentiated NEC, with a Ki67 >20%, are associated with worse prognosis [2].

The most common metastatic sites of NETs are the lymph nodes, liver and lung. Cutaneous metastases are considered rare. Only 28 articles were accessed, totaling 31 cases, which are summarized in table 1. There was a slight prevalence in men (16/31), with a mean age of 55 years at the time of diagnosis (ranging from 19 to 82 years). In most cases, the lesions were single or multiple nodules, nonulcerated, painless, of slow growth, ranging from 0.5 to 2.5 cm in diameter and clinically unspecific like other cutaneous metastasis. The location was most frequently on the cephalic segment (typically on the scalp) and/or trunk. We call attention to two distinct cases: (1) painful spots referred by the patient without visible or palpable cutaneous lesions; (2) single hardened lesion on the eyelid, simulating the primary cutaneous lesion [8–35].

Most of the cases presented with painless lesions, although in some patients the lesions can be painful. In this context, primary painful cutaneous tumors are important differential diagnoses. They can be easily remembered by the acronym LEND AN EGG (leiomyoma, eccrine spiradenoma, neuroma, dermatofibroma, angiolipoma, neurilemmoma, endometrioma, glomus tumor and granular cell tumor) [36].

Prognosis is not good. The 5-year survival rate is 19% for patients with metastatic NEC [3]. Despite chemotherapy, an effort should be made for the identification of the primary site, since its resection will increase the disease-free survival and allow appropriate chemotherapy [7].

Conclusion

Cutaneous metastases of NEC are rare, but it is important to emphasize the relevance of the dermatologist in such cases. Clinical suspicion and histopathology diagnosis permitted the identification of the disease progression, which was a determinant factor for modifying the chemotherapy protocol.

Statement of Ethics

Our patient gave his written authorization for the publication of his case, and the authors followed all ethical guidelines.

Disclosure Statement

The authors declare no conflicts of interest.

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Table 1. Cases of cutaneous metastasis of NEC found in PubMed

First authors [Ref.], year	Age, years	Gender	Primary site	Lesion type and location
Reingold [9], 1960	35	M	Lung	Subcutaneous nodules; diffusely distributed, except face, hands and feet
Bean [10], 1968	62	M	Unknown	Multiple nodules in a dome format; scalp and anterior trunk
Colin-Jones [11], 1969	73	F	Pancreas	Painless nodules; abdomen and limbs
Sullivan [12], 1981	19	M	Testicles	Nodules; trunk
Archer [13], 1985	68	F	Lung	Subcutaneous nodules, cervical region; trunk and thighs
Rodriguez [14], 1992	80	M	Stomach	Subcutaneous nodules; forehead, posterior cervical region, trunk and thighs
Schmidt [15], 1994	63	F	Larynx	Painful nodules, diffusely distributed on the body
Grunewald [16], 1996	62	F	Gastrointestinal tract	Nodule; umbilical scar
McCracken [17], 1996	67	M	Gastrointestinal tract	Hard nodule; left superior eyelid
Ereño [18], 1997	72	F	Larynx	Hard nodules; scalp
De Argila [19], 1999	71	M	Lung	Single pinkish erythematous nodule with superficial erosion; face
Ottinetti [20], 2003	61	M	Larynx	Hard erythematous violaceous nonulcerated nodules; trunk
Zhang [21], 2003	34	F	Pancreas	Hard nodule; periumbilical
Bell [22], 2005	69	M	Rectum	Multiple subcutaneous nodules
Vidulich [23], 2007	76	F	Breast	Nodules in annular disposition, in contiguity to a breast tumoral mass
Santi [24], 2008	60	M	Lung	Erythematous violaceous nodule, with rapid growth; dorsum
Chung [25], 2008	31	F	Uterus	Two erythematous purpuric nodules; scalp
Lee [26], 2009	20	M	Bladder	Single erythematous dome format nodule with central ulceration; scalp
Simpson [27], 2009	82	M	Larynx	Painful erythematous papules and nodules; head, neck and trunk
Blochin [28], 2010	55	F	Lung	Painful points, without visible erythema or palpable nodule; scalp
Yu [29], 2010	50	F	Lung	Single subcutaneous nodule; right axilla
Sanii [30], 2011	79	F	Thyroid	Multiple erythematous painful nodules and plaques; right forearm, abdomen and back
Boyd [31], 2012	50	F	Breast	Erythematous papules and nodules over the skin of the reconstructed left breast
Fluehler [32], 2013	65	M	Gastrointestinal tract	Single erythematous nodular lesion with telangiectasias; face
Yuan [33], 2014	60	F	Lung	Single erythematous nodular lesion on the breast
Ishida [34], 2014	55	M	Lung	Single subcutaneous nodule; scalp
Wang [35], 2014	62	M	Gastrointestinal tract	Multiple subcutaneous nodules; scalp
Jedrych [8], 2014	50	F	Lung	Single painless nodule, nonulcerated, slow progressive growth; scalp
	74	M	Lung	Single painless nodule, nonulcerated, slow progressive growth; scalp
	67	F	Pancreas	Single painless nodule, nonulcerated, slow progressive growth; scalp
	67	F	Gastrointestinal tract	Single painless nodule, nonulcerated, slow progressive growth; dorsum

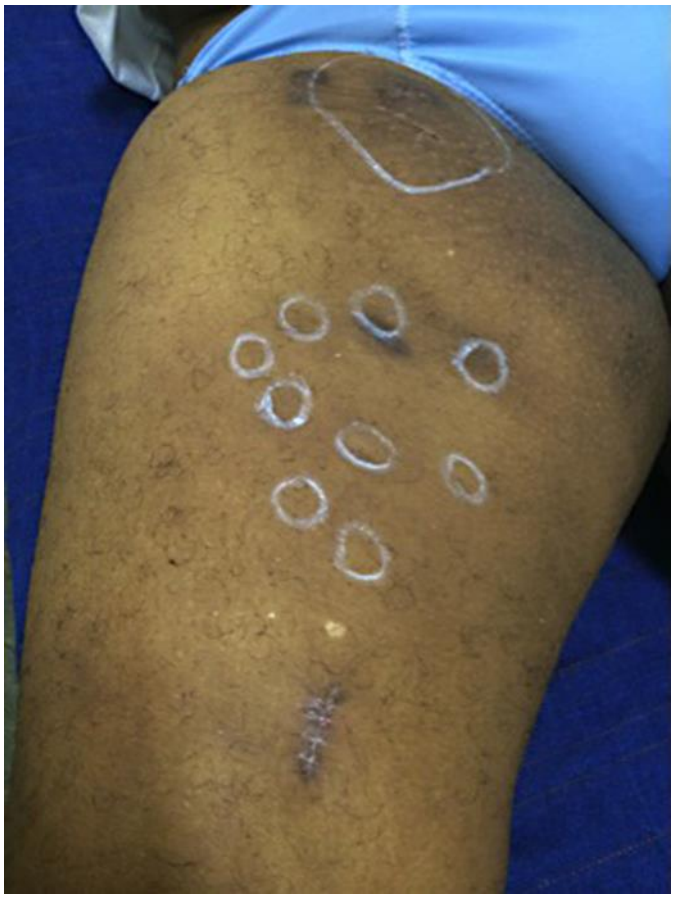

Fig. 1. Marking of the site of the inguinal lymph node previously excised and, in the smaller round markings, the nodular subcutaneous lesions on the right thigh.

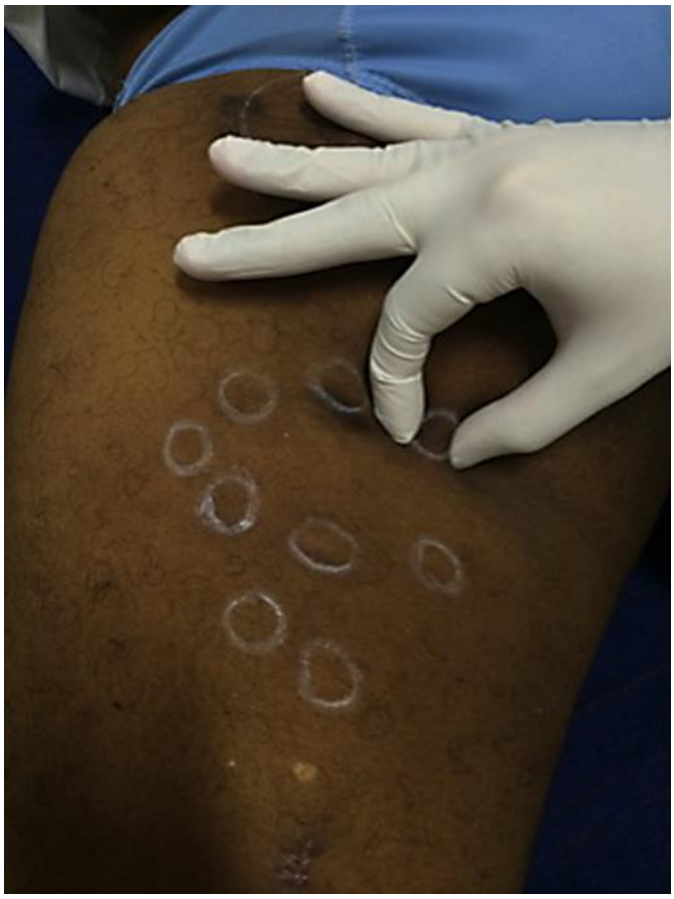

Fig. 2. Palpation of the nodular subcutaneous lesion on the right thigh (in detail).

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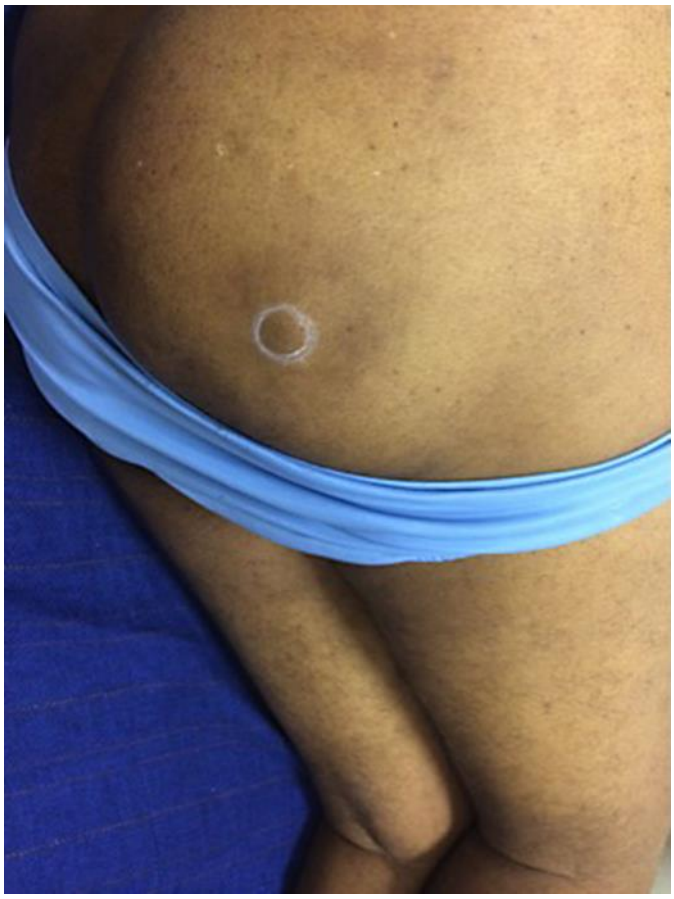

Fig. 3. Nodular isolated lesion on the right buttock.

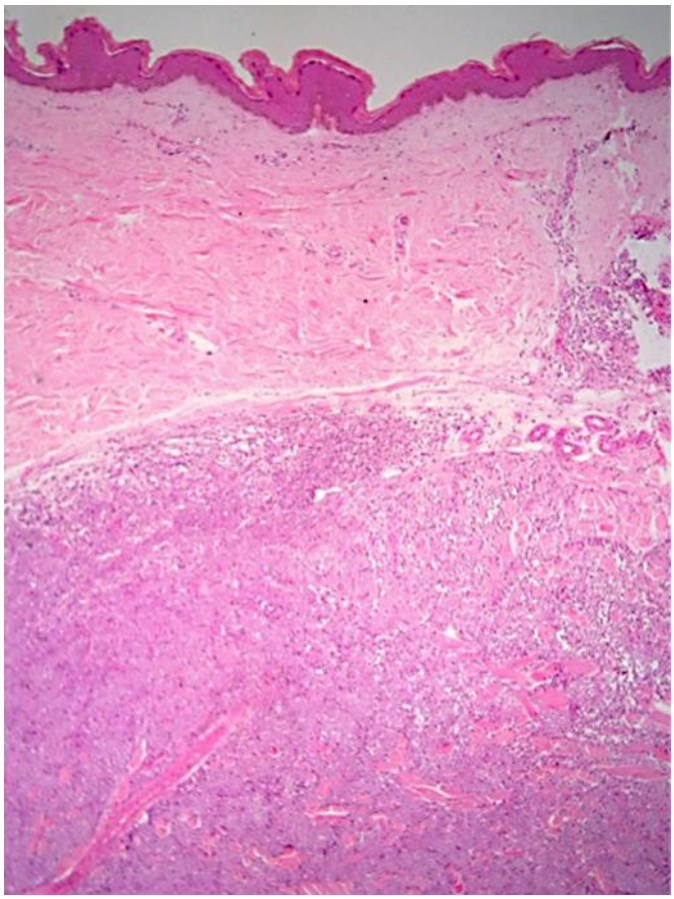

Fig. 4. Nodular lesion on the dermis and hypodermis. HE. ×40.

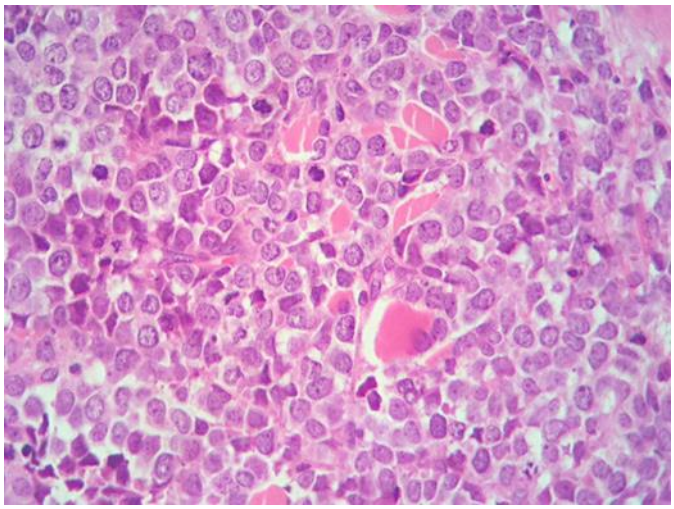

Fig. 5. Monomorphic proliferation of cells with poorly defined cytoplasmic borders and round nucleus with uniformly distributed fine granular chromatin. HE. ×400.

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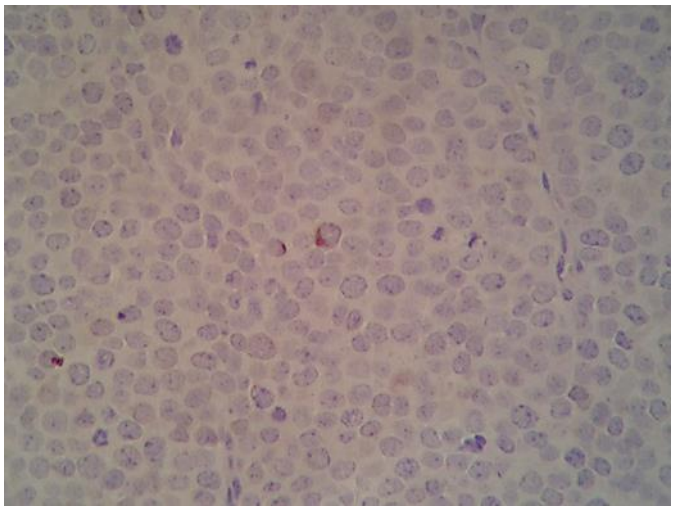

Fig. 6. Focal positivity in dot for CK20. CK20. ×400.

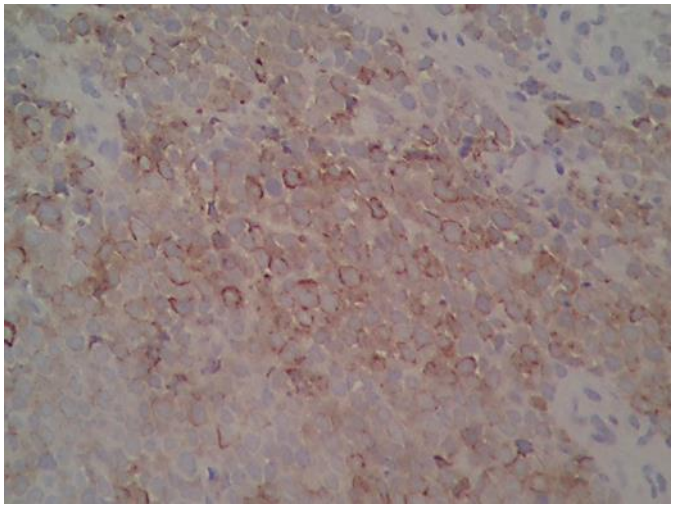

Fig. 7. Positivity for Chromogranin. Chromogranin. ×400.

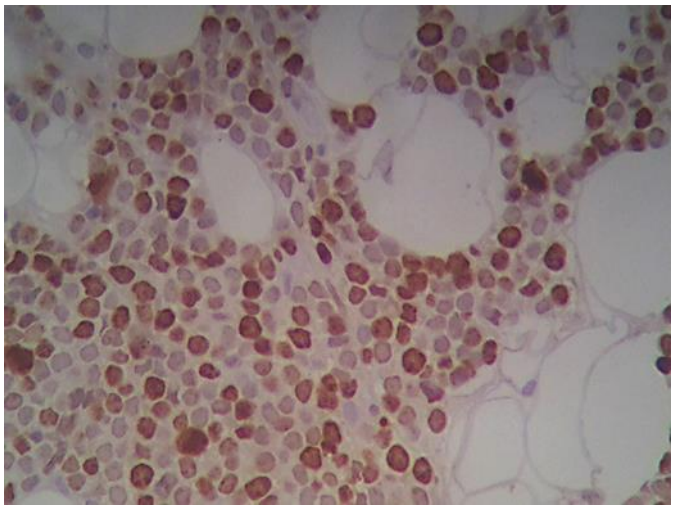

Fig. 8. Positivity for Ki67 (MIB-1) of about 60%. Ki67. ×400.