Neuroendocrine tumor arising de novo in the left upper thigh: a case report

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Abstract
Neuroendocrine tumors (NETs) originate in the neuroendocrine cells of the neural crest (Kulchitsky cells). If neuroendocrine tumors arising in the digestive tract or lung may occasionally result in skin metastases, primary soft tissue or skin NETs are infrequent. The current paper presents the case of an elderly woman patient with neuroendocrine tumors arising de novo in the left upper thigh, accompanied by lymph nodes metastases in the left groin and in the left pelvic sidewall, in close vicinity of the iliac vessels. The diagnosis of NET was performed based on immunohistochemical tests. Such tumors show a slow growth and, generally, have a good prognosis. It is emphasized that complete surgical excision, in some cases associated with adjuvant external radiotherapy is the optimal therapeutic modality in dealing with such lesions.

Keywords: neuroendocrine tumors, soft tissue, skin.

Introduction
Neuroendocrine tumors (NETs) are tumors that exhibit an extremely variable clinical and biological behavior, depending on the location, degree of differentiation and their secretory activity, being able to secrete and store peptides and neuroamines [1, 2].

Also known as carcinoid tumors, these tumor cells are characterized by the presence of neurosecretory granules that express specific markers, including neuron-specific enolase (NSE), synaptophysin and chromogranin [3].

In some cases, the tumor cells release serotonin and other vasoactive substances in the systemic circulation, which may account for the occurrence of the carcinoid syndrome.

This carcinoid syndrome is often associated with the existence of liver metastases.

In the case of neuroendocrine tumors, regardless of their location, skin metastases are occasionally cited, more often than not, coexisting with other metastatic localizations [4, 5].

Primary neuroendocrine tumors arising in the skin or in the soft tissue are extremely rare.

In this context, we focus on the case report of an elderly woman patient with neuroendocrine tumor arising de novo in the left upper thigh.

Case report
The patient SN, aged 77 years, from Craiova, Romania, was referred to the clinic with a three months history of a moderately growing subcutaneous mass in her left upper thigh.

On physical examination, a 5/6 cm hard subcutaneous mass in the left upper thigh with the normal overlaying skin was revealed. There was also palpable lymph nodes enlargement in the left groin.

The patient had no systemic symptoms such as flushing, wheeze or diarrhea.

Her past medical history included hypertension, ischemic stroke and ischemic coronary disease, with 3rd class NYHA (New York Heart Association) heart failure. An X-ray of the thorax indicated obvious signs of emphysema.

The laboratory tests pointed to normal values and the tumor markers such as CEA (carcinoembryonic antigen), CA125 and CA19-9 were not elevated: hemoglobin 12.45 g/dL, WBC (white blood cell) count 10.21×1000 cells/μL, CEA 0.777 ng/dL, CA125 10.38 U/mL, CA19-9 12.83 U/mL.

The given markers such as CEA, CA125, CA19-9 were tested in order to exclude a malignant ovarian or digestive pathology, which could be responsible for the patient’s clinical picture.

CT scans of the chest, abdomen and pelvis showed lymph nodes enlargement in the left groin and left pelvic sidewall, in close vicinity of the iliac vessels, but no pathology in the lungs or liver.

Intraoperatively we found a 6 cm hard tumor in its greatest diameter, with close adhesion to the skin and with an important extension to the anterior muscles of the thigh (rectus femoris, Sartorius and vastus medialis).

The tumor resection was followed by left inguinal dissection, seven nodes being removed.

Taking into consideration the patient’s general condition, radical surgery (including left iliac nodes dissection) was, in our opinion, too risky.
The microscopic exam showed the presence of diffuse infiltrate with a relative monomorphic malignant cell proliferation constituted by a population of a small sized, cubical cells separated by a subtle fibrovascular stroma responsible for either an insular or a trabecular loose appearance. The almost monomorphic tumor cells displayed irregular round or oval nuclei with patches of fine granular cytoplasm, a “salt and pepper” stippled chromatin and rare atypical mitoses. Large foci of necrosis were also noteworthy. Metastases were detected in two of the regional lymph nodes under examination.

The immunohistochemical investigation revealed that the tumor cell cytoplasm stained diffusely and positively for the presence of both chromogranin A (with a granular cytoplasmic appearance) and CD56 (at the cellular membrane level) or NSE (as demonstrated by the specific immune discoloration of the cytoplasm). On the other hand, pancytokeratin (AE1/AE3) was immunomarked like perinuclear “dots” in the cytoplasm of the tumor cells. The proliferation index Ki67 was demonstrated in up to 65% of the malignant cells nuclei.

Postoperatively, 24 h urinary 5-HIAA (5-hydroxyindoleacetic acid) concentration was normal. Following excision, the patient was treated by external beam radiotherapy to the high upper thigh, to the groin and to the left side of the pelvis.

Six months later, the CT scan revealed no residual inguinal or pelvic sidewall pathology.

**Discussion**

Soft tissue or skin involvement in NETs, either primary or secondary metastatic spread, is extremely rare [6].

Out of the 10 previously reported cases of such primary tumors up to 2007, eight arose de novo in the skin, another case presented as a subcutaneous mass in the foot, and the last originated in thigh muscles [3].

The majority of the primary neuroendocrine tumors originating in the skin are located in the trunk and scalp [3].

Unlike primary neuroendocrine tumors, which are unique, skin or soft tissue metastases, generally arising in the gastrointestinal tract or the tracheobronchial tree, are small (1–2 cm), multiple and often accompanied by clinical signs generated by the primary tumor (digestive and respiratory symptoms, etc.) [4–7].

In the case of our patient, symptomatology was absent, the only clinical sign being the subcutaneous mass in the left upper thigh, moderately growing for three months,
and associated with palpable lymph nodes enlargement in the left groin.

Conventional imaging techniques as well as the CT scan performed in our case or MR1 or ultrasound reveal the primary tumor, its anatomical relations, the lymph node extension or the distant metastases.

In the case of small primitive tumors, their identification by such techniques can be difficult [8].

Under these circumstances, 123I-mIBG (metaiodobenzylguanidine) scan may be used, which shows a sensitivity and specificity of 60% in identifying neuroendocrine tumors; alternatively, the octreotide scan shows a sensitivity ranging between 72–87%, but the specificity is lower [9, 10].

Histopathological examination may suggest a neuroendocrine tumor, but the diagnosis is confirmed by immunohistochemical examination. Immunohistochemical studies were performed with Streptavidin–Biotin complex method (LSAB), using a panel of antibodies against the following antigens: cytokeratin (Mo Ab clone AE1/AE3), chromogranin, NSE, CD56, Ki67. Neuroendocrine tumor cells showed strong and diffuse positive staining for chromogranin A, cytokeratin, NSE, CD56 [11, 12]. We can say that the final diagnosis of the neuroendocrine tumor, in our case, was based on a combination of characteristic morphology and neuroendocrine phenotype as demonstrated by immunohistochemical staining.

The cutaneous neuroendocrine tumors arising in the Kulchitsky cells (NETs) should be distinguished from other cutaneous tumors arising from Merkel neurosecretory cells [13].

From the histological point of view, the Merkel neurosecretory cells display a diffuse tumoral growth with a seldom trabecular pattern whereas the tumor cells appear rounded and small in size due to a scarce cytoplasm while their nucleus is vesicular and round is shape with multiple nucleoli and a fine dusty granular chromatin; the tumoral stroma contains vascular proliferations with rounded endothelial cells.

Both NETs and Merkel cell carcinomas (MCC) can show specific stains for neuroendocrine markers such as chromogranin or synaptophysin, but in the case of MCC tumors, these stains show variable positivity for cytokeratin in contrast to the more diffuse staining seen in NETs [14, 15].

Merkel cell tumor usually reacts immunologically for perinuclear cytokeratin especially under the form of “globs” rather than “dots” (quite suggestive for a neuroendocrine tumor) and thus the large size of these perinuclear cytokeratin globes becomes a helpful clue to the diagnosis (of Merkel cell tumor).

The skin and soft tissue primary NETs show a slow growth towards tissue structures in close vicinity or locoregional lymph nodes seldom generating distant metastases.

The therapeutic attitude in our patient, first involved surgical excision of the primary tumor combined with groin nodal clearance.

Taking into consideration the existence of pelvic nodes in close vicinity of left iliac vessels, some nodes are possible carriers of secondary lesions, which, due to objective reasons, could not be removed, and postoperatively, external beam radiotherapy was undertaken.

In our case, the primary tumor was considered aggressive, as suggested by the diffuse positive staining for the immunohistochemical marker Ki67, radiotherapy was extended to the tumor in the upper left thigh and left groin.

The quantitative assessment of Ki67 reactive cells could help us to determine prognosis and survival, a Ki67 index of 65% predicting an aggressive development [3].

Despite the aggressiveness of the tumor bed, radiotherapy has proven effective with no residual pelvic sidewall, and the patient remaining free of recurrence at six months follow-up.

According to the literature, radiotherapy has been used successfully in unresectable NETs, disease regression and symptom palliation being achieved in the majority of cases [16, 17].

Unlike Merkel cell carcinomas (MCC), which are considered aggressive tumors, frequently generating local recurrences, nodal and distant metastases, when the average survival is of only five months, prognosis is more favorable in the case of cutaneous or soft tissue primary NETs [18, 19].

Survival at five years follow-up in the case of cutaneous or soft tissue primary NETs decreases from 70% in patients with no metastases to less than 50% in patients with regional or distant metastases [20–23].

Conclusions

Skin or soft tissue primary neuroendocrine tumors are extremely rare, 10 cases being published until 2007, so we consider this case report opportune. These tumors show a good prognosis, but in our case, a Ki67 index of 65% predicts an aggressive development. Complete surgical excision associated in some cases with adjuvant radiotherapy is the optimal therapeutic modality in dealing with such lesions.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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