Soft Tissue Primary Neuroendocrine Tumor: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient:	**Male, 48**
Final Diagnosis:	**Neuroendocrine tumor**
Symptoms:	**Abdominal pain**
Medication:	**—**
Clinical Procedure:	**Excision of the tumor**
Specialty:	**Surgery**

Objective: Rare disease

Background: Neuroendocrine tumors found in skin or soft tissues usually represent metastasis from other organs and are considered late manifestations of disease. Therefore, primary cutaneous and soft tissue neuroendocrine tumors are extremely rare.

Case Report: We report a case of a 48-year-old male with a neuroendocrine tumor occurring in the subcutaneous abdominal fat, which had an echographic appearance of a vascular malformation. The finding was diagnosed as compatible with neuroendocrine tumor based on histopathological and immunohistochemical studies. No other sites of possible internal origin were detected on supplementary investigations.

Conclusions: Soft tissue neuroendocrine tumors may have an appearance on imaging studies that challenge physicians to make a correct diagnosis. Despite the rarity of these tumors, they should be included in the differential diagnosis of other soft tissue masses.

MeSH Keywords: Neoplasms, Connective and Soft Tissue • Neuroendocrine Tumors • Skin Neoplasms

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Background

Neuroendocrine tumors (NETs) are rare tumors that originate in neuroendocrine cells. These cells are mostly of neural crest origin and are widely distributed in the body. The most common NETs are those of the gastroenteropancreatic system (73.7%), followed by tracheobronchopulmonary NETs (25.1%) [1]. Other sites are seldom affected but include parathyroid, adrenal, and pituitary glands, and calcitonin-producing cells of the thyroid [2]. NETs found in skin or soft tissue usually represent metastases from other organs and are considered late manifestations of disease [3,4]. Primary cutaneous and soft tissue neuroendocrine tumors are extremely rare, as shown by a lack of their description (except for Merkel cell carcinoma of the skin) in The World Health Organization books on skin and soft tissue tumors [5–7]. Only a few case studies of soft tissue NETs are available in the literature [8–11]. This case study presents our experience with an unusual case of abdominal subcutaneous primary NET with atypical ecographic findings.

Case Report

A 48-year-old male presented to our emergency room complaining of a sharp, needle-like pain, 2 cm to the left of the umbilicus. The patient reported that the pain had started 2 years prior to presentation, occurred occasionally, with growing intensity and with no correlation to any known triggering factors. He had not experienced flushing attacks, diarrhea, or wheezing. He had not suffered from any other illnesses. Colonoscopy and superior digestive endoscopy performed in other medical units described normal appearance of his examined digestive tract.

On physical examination of the abdomen, the pain was aggravated on palpation of the left periumbilical region, but no mass or sign of tenderness was found. Physical inspection of other body parts revealed no abnormalities. Blood analyses showed insignificant elevation of fibrinogen (413 mg/dL); other values (full blood count, liver function, iron levels, urea and creatinine, electrolytes, albumin, total protein, creatinine kinase, total cholesterol) were in normal ranges.

Ultrasound examination was made using a 5–12 MHz linear-array transducer and revealed a small, 7.9/4 mm in diameter, hypoechoic image with hyperechoic margins, situated in subcutaneous fat, 7 mm in depth from skin demarcation. The tumor was painful on compression. On color Doppler analysis, it had an appearance of vascular bundle with arterio-venous mixed signal. An arterial branch that converged to the malformation could be detected (Figures 1, 2). As the lesion was thought to be a soft tissue vascular malformation, no other diagnostic imaging techniques and no biochemical screening for 24-hour urinary 5-HIAA or plasma chromogranin A levels were performed. Excision of the tumor was carried out under general anesthesia; intraoperatively it had the appearance of a subcutaneous nodule of approximately 7.9/4 mm in diameter and was red in color. The tumor was removed with wide margins of resection

Histopathological examination revealed a subcutaneous nodule highlighting, microscopically, a cellular insular proliferation, with cohesive polygonal cells with finely granular, eosinophilic cytoplasm, with round, small, normo- and hyperchromatic, monomorphic nuclei, and with a mitotic count suggestive of well- to moderately-differentiated neuroendocrine tumor. The adipose tissue around it contained foci of unspecific chronic inflammation and fine septa of collagen.

On immunohistochemical analysis, the cytoplasm stained focally positive for the presence of chromogranin and diffusely positive for synaptophysin. On the other hand, the tumor cells were negative for pancytokeratin (AE1/AE3), neural cell adhesion
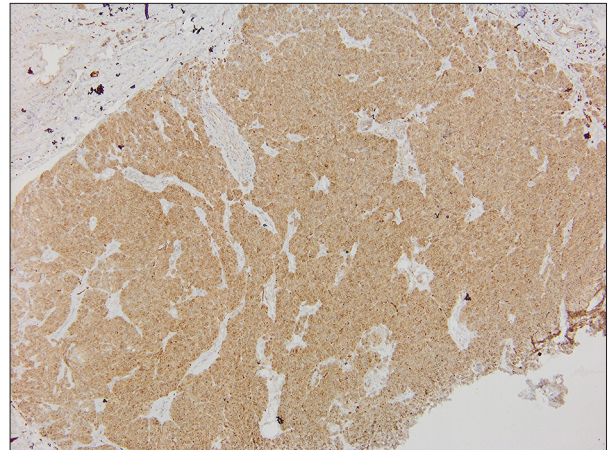

Figure 1. Soft tissue ultrasound scan showing depth of tumor localization from the skin surface (red mark).
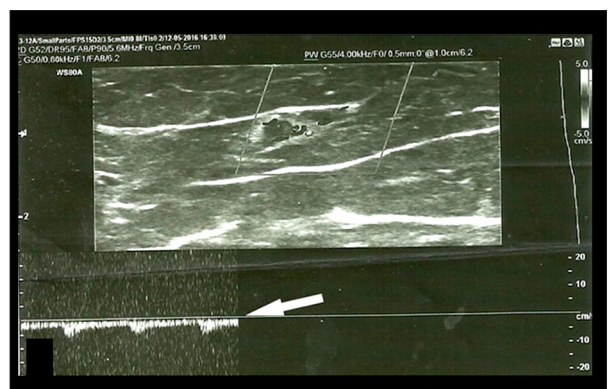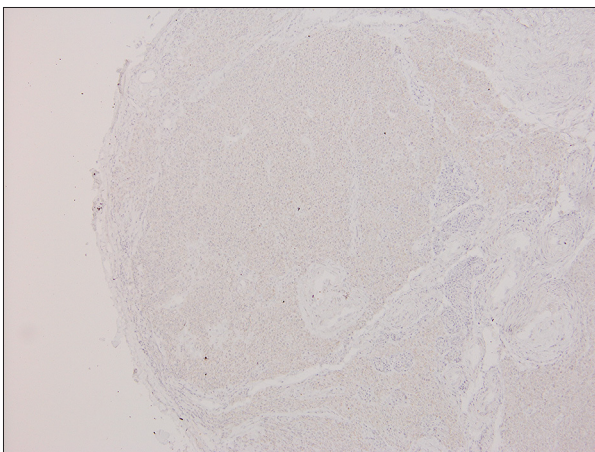

Figure 2. Doppler echography scan: tumor appearing in the shape of a vascular bundle. White arrow: positive Doppler signal can be noticed.
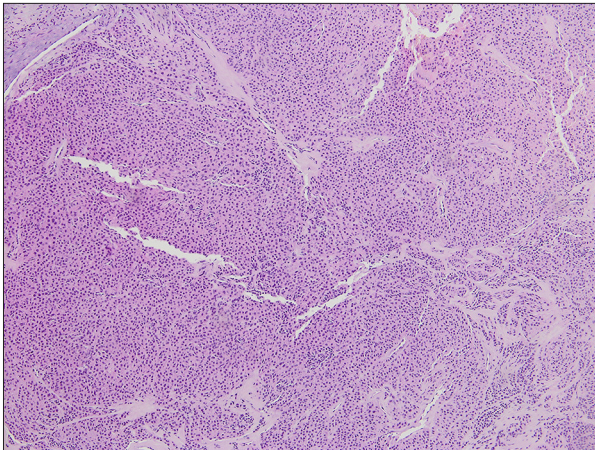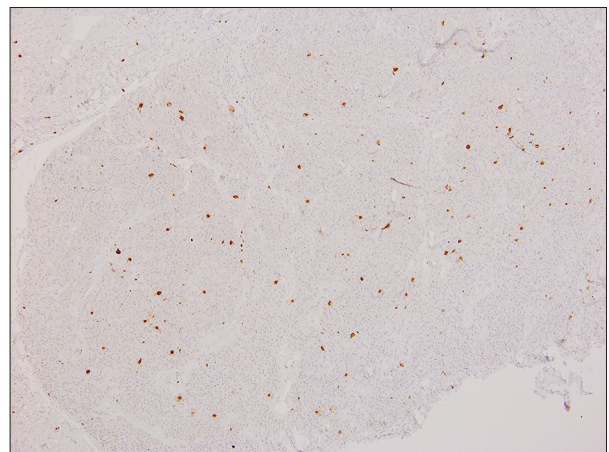
Figure 3. Polygonal cells with insular arrangement (hematoxylin and eosin 10×).

Figure 5. Synaptophysin diffuse positivity (10×).

Figure 4. Chromogranin focal positivity (10×).

Figure 6. Ki-67 index moderate positivity (10×).

molecule (NCAM/CD56), and CD99, CK20, and CK7 markers. Ki67 showed a proliferative index of 3–4% (Figures 3–6).

The patient's postoperative recovery was uneventful. Taking into consideration the possibility that the subcutaneous tumor was a metastasis from an intraabdominal site, computed topography (CT) scans of thorax, abdomen, and pelvis were performed in the recovery period, 6 months and 1 year after the operation. No other tumors in the body were found. Biochemical analyses after 1 year of follow-up were in normal ranges.

Discussion

NETs peculiarity lies in its ability to produce peptides, which cause characteristic hormonal syndromes. NETs display functional and nonfunctional symptoms and are generally classified as foregut, midgut, and hindgut according to their embryonic origin [12]. Their overall incidence is estimated to be of 5.25 per 100 000 people [2].

The differential diagnosis of primary painful skin and subcutaneous nodules of abdominal wall includes pilar cyst, neurofibroma, and sebaceous cyst [13–15]. Other important pathologic entities that histologically can resemble primary neuroendocrine cutaneous tumors are Merkel cell carcinoma, sebaceous neoplasms and melanoma with carcinoid-like architecture, endocrine mucin producing sweat gland carcinoma, and primary skin tumors with neuroendocrine differentiation [16]. Furthermore, NETs of skin and subcutaneous tissue may represent primary cutaneous disease, either as metastatic from primary neuroendocrine disease elsewhere in the gastrointestinal tract or in the lungs [17]. Skin metastases are usually multiple [18].

In making a positive diagnosis of skin and subcutaneous primary NETs, neither clinical findings nor imaging results are pathognomonic. Nevertheless, 13 previous case reports of skin primary NETs have described the lesions as being located on the trunk or scalp and presenting as single, firm, fixed to the skin, flesh-colored, non-ulcerated cutaneous nodules, ranging from 0.9–9.5 cm in diameter [6,16,19–21]. Only 7 articles were

available that reported on soft tissue primary NETs mostly affecting thigh, breast, or axilla [9–12,22–24]. The particularity of our case lies in its unusual periumbilical location and in presenting as a painful spot, without any visual or palpable lesion. Pain in some cases can be due to infiltration of nerve bundles by tumor deposits [5]. No nerve involvement was seen on histopathological exam of our case.

Identifying small primary NETs might be a challenge with conventional imaging techniques. According to the report of Berge and Linell, who evaluated 16 294 autopsies and 44 surgical specimens in Malmo between 1958 and 1969 and declared a carcinoid incidence of 8.4 per 100 000 population per year, it is likely that a significant percentage of carcinoid tumors remain asymptomatic and undetected during a person's life time [25,26].

Transabdominal ultrasonography is often the first technique utilized for NET imaging, based on its non-invasiveness and accessibility [27]. Soft tissue NETs appear as well-defined hypoechoic

masses with internal heterogeneous echotexture and increased vascularity [12]. In our case, ultrasound Doppler view revealed an appearance of vascular bundle with arterio-venous mixed signal and was erroneously thought to be a vascular malformation.

Supplementary investigations, such as superior and inferior digestive endoscopy, bronchoscopy, CT scans, and magnetic resonance imaging (MRI), are useful to exclude a possible primary site of soft tissue NETs. While CT scans and MRIs display a kindred appearance of intraabdominal NETs [28], somatostatin receptor scintigraphy with indium-111 labeled octreotide and iodine-metaiodobenzylguanidine scintigraphy proved their superiority in localizing the primary tumor site [25,29,30]. Taking into consideration the long course of the disease in our case (2 years) and the generally aggressive course of gastrointestinal tumors with skin metastases, it is unlikely that a primary site was omitted on CT scans of this patient.

As for biochemical analyses, Baudin suggested that chromogranin A ought to be the only general marker screened in NET patients [31]. Because ultrasound result did not raise suspicion of NET, in our patient case, chromogranin A was not measured in the blood.

Most neuroendocrine tumors fall into 3 broad histologic categories: well-differentiated, low-grade (G1); well-differentiated, intermediate-grade (G2); and poorly differentiated, high-grade (G3) [32].

Final positive diagnosis is made by histopathological analyses and immunohistochemistry. Tumor cells denote positive reactions to silver stains and to markers of neuroendocrine differentiation, includingneuron-specific enolase, synaptophysin and chromogranin. The last two are considered to be the most relevant [2,32].

Primary NETS of the skin should be distinguished from Merkel cell carcinomas of the skin that has features of aggressive neoplasia: rapid growth, ulceration, significantly increased nuclear to cytoplasmic ratio, brisk mitotic and apoptotic activity, nuclear molding, and necrosis [8]. Moreover, CK20 staining in Merkel cell carcinoma has a characteristic perinuclear punctate or dot-like pattern of positivity, which is completely absent in well-differentiated skin NETs [11]. Plus, the skin of our patient remained intact, the lesion being localized 7 mm in depth from skin demarcation.

Negative staining for CD99 helps in the differential diagnosis with primary malignant peripheral primitive neuroectodermal tumor [33].

Proliferation index for Ki67 of 3–4% of the tumor in our case suggests that the tumor is an atypical carcinoid with some malignant potential. It is not considered suggestive of a neuroendocrine carcinoma because the last one has a Ki67 more than 20% and a higher mitotic count [6].

The elective treatment in soft tissue NETs is surgical excision, combined in some cases with local lymphadenectomy [15]. For patients who are not fit for surgery, treatment choices for non-resectable disease include interferon-α and long-acting somatostatin analogues, radiotherapy, ablation therapy, and chemotherapy [34,35]. In our case, taking into consideration the tumor's small size and no adenopathies detected on clinical examination or on echography, local wide excision without lymphadenectomy was performed.

The slow course of the disease (2 year before surgery) and no evidence of recurrences after 1 year of follow-up permits us to think that our case was a primary soft tissue NET with a good prognosis.

Conclusions

Primary soft tissue NETs are rare conditions with an echographic appearance that makes it hard to differentiate them from other tumors. They can be easily confused with a vascular malformation, as happened in our case. Careful preoperative examination and laboratory analysis should be made in order to achieve the appropriate diagnosis.

Acknowledgements

Conflict of interest

None.

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