Skin Involvement of Metastatic Neuroendocrine Tumour in a Black African: A Rare Occurrence

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ABSTRACT

Neuroendocrine tumours (NETs) constitute an infrequent group of neoplasms arising from neuroendocrine cells present in most body parts. They represent about 0.5% of all cancers and commonly affect the middle-aged and the elderly. While metastatic NETs are generally rare, skin metastasis is extremely rare and is a poor prognostic factor. Unfortunately, most cases are diagnosed at the late stage of the disease, thus making effective management difficult. We present a case of metastatic NET of unknown origin with skin deposits in a black African woman in a resource-limited setting. This case highlights the importance of considering cutaneous metastasis of NETs in patients of advanced age presenting with skin nodules.

Keywords: Neuroendocrine, Tumour, Skin metastasis, Black African

Atteinte Cutanée d'une Tumeur Neuroendocrine Métastatique chez un Africain Noir : un Evénement Rare

Les tumeurs neuroendocrines (TNE) constituent un groupe peu fréquent de néoplasmes provenant de cellules neuroendocrines présentes dans la plupart des parties du corps. Ils représentent environ 0,5 % de tous les cancers et touchent généralement les personnes d'âge moyen et les personnes âgées. Si les TNE métastatiques sont généralement rares, les métastases cutanées sont extrêmement rares et constituent un facteur de mauvais pronostic. Malheureusement, la plupart des cas sont diagnostiqués à un stade avancé de la maladie, ce qui rend difficile une prise en charge efficace. Nous présentons un cas de TNE métastatique d'origine inconnue avec une atteinte cutanée à type de nodule chez une femme noire africaine dans un environnement aux ressources limitées. Ce cas met en évidence l'importance d'évoquer les métastases cutanées des TNE chez les personnes âgées présentant des nodules cutanés.

Mots-clés : Neuroendocrinien, Tumeur, Métastases cutanées, Afrique noire

INTRODUCTION

Neuroendocrine cells are precursors of neuroendocrine tumours and are found in most parts of the body. The incidence of NETs varies with geographical location, with a rate of 1-2 cases/100,000 inhabitants per year in the United States of America and Europe.[1] It has an approximated prevalence rate of 35/100,000 inhabitants.[2] NETs may be slow-growing or aggressive. The most common metastatic sites are the lymph nodes, liver, and lung. Skin metastases are considered rare.[1,3]

No available data exist regarding the prevalence of cutaneous metastasis of NETs, probably due to its rarity. In 2017, Andres et al.[4] reported the 43rd case of skin metastasis of NETs in the English literature.

Patients with NETs may be asymptomatic, with the tumour being detected as an incidental finding in the early stage of the disease. When symptoms develop, they can vary based on the location of the tumour. In rare cases, skin flushing, diarrhoea, or fluctuating blood glucose levels may be experienced depending on whether the tumour is functional or not.[5] Dermatologists should consider endocrine neoplasms when skin nodules are present with certain other associated signs.

We present a case of metastatic NET of unknown origin with skin deposits in a black African woman in a resource-limited setting. This case highlights the importance of considering cutaneous metastasis of NETs in patients of advanced age presenting with skin nodules.

CASE

A 68-year-old black Nigerian woman presented to the emergency unit with the complaint of progressive weight loss, recurrent diarrhoea, right eye pain, and

features of anaemia of three months duration. Two weeks prior to presentation, she developed painless nodular swellings on her trunk and an inability to bear weight on the right lower limb with associated right hip pain of three days duration.

General examination revealed an acutely ill-looking elderly woman in painful distress, pale, icteric with no significant peripheral lymphadenopathy. There was bilateral pitting pedal oedema up to the knee. The right eye showed an absent perception of light, marked ptosis, and haemorrhagic chemosis.

She had multiple dome-shaped subcutaneous nodules over the trunk, with sizes ranging from 10.0mm to 25.0mm. They were of normal overlying skin colour, non-tender, firm, smooth-surfaced, and well-demarcated [figure 1]. Musculoskeletal examination showed an oedematous right hip with differential warmth and tenderness.

The right lower limb was externally rotated with shortening and a positive leg rolling test. Pelvic x-ray showed features in keeping with pathological left femoral neck fracture [figure 2].

A histopathological report on one of the excised nodules revealed an infiltrative tumour dispersed in nests separated by thin fibrovascular septae. The comprising cells have indistinct cellular margins, fairly uniform round to oval nuclei, fine chromatin patterns, and moderate eosinophilic cytoplasm. Frequent atypical mitosis, lymphovascular invasion, and extensive areas of necrosis were seen. The stroma was moderate and fibro-collagenous.

A histopathological diagnosis of a metastatic malignant neuroendocrine tumour of unknown origin was made [Figures 3 and 4].

Abdominopelvic ultrasonography revealed ascites and hepatic metastasis. Liver function tests demonstrated hyperbilirubinaemia and elevated alkaline phosphatase. Her CEA – was 0.095ng/ml, and her haemoglobin was 8g/dl.

A working diagnosis of a malignant neuroendocrine tumour of unknown primary with metastasis to the skin, bone, liver, and right eye involvement was entertained.

A multidisciplinary approach was adopted in her management with the goal of palliation. She had blood transfusions, was placed on analgesics, DVT prophylaxis, stabilized her right lower limb, and other forms of palliative care.

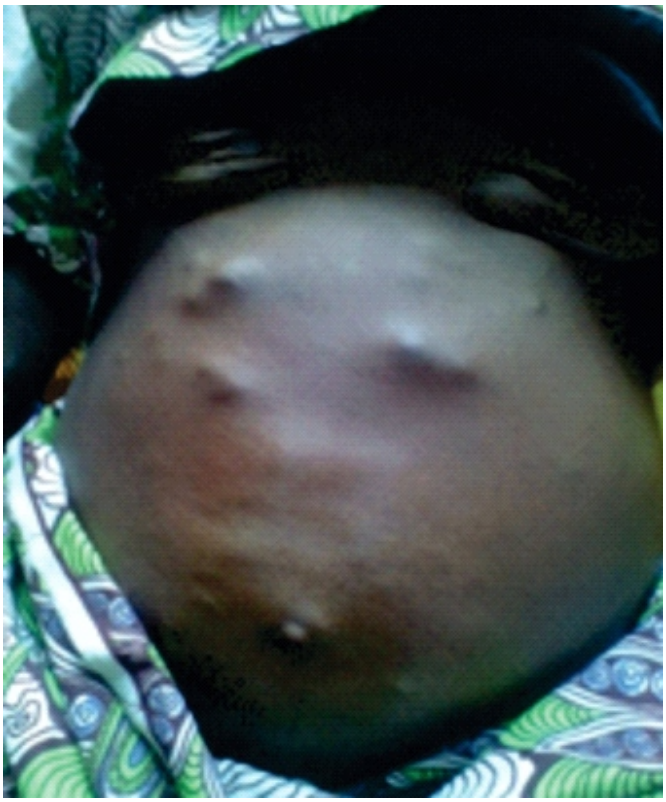

Figure 1: Multiple Anterior Abdominal Wall Nodules

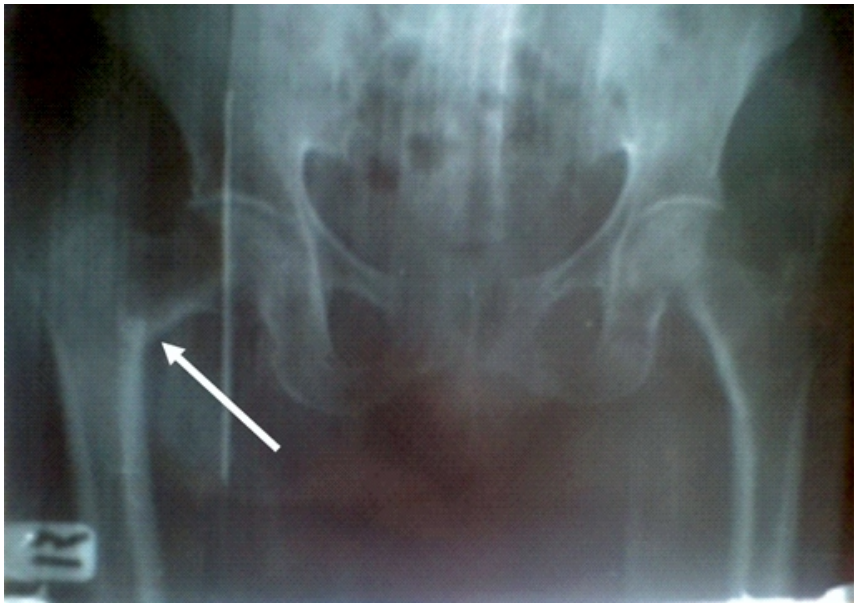

Figure 2: Pathological Fracture of Neck of Right Femur

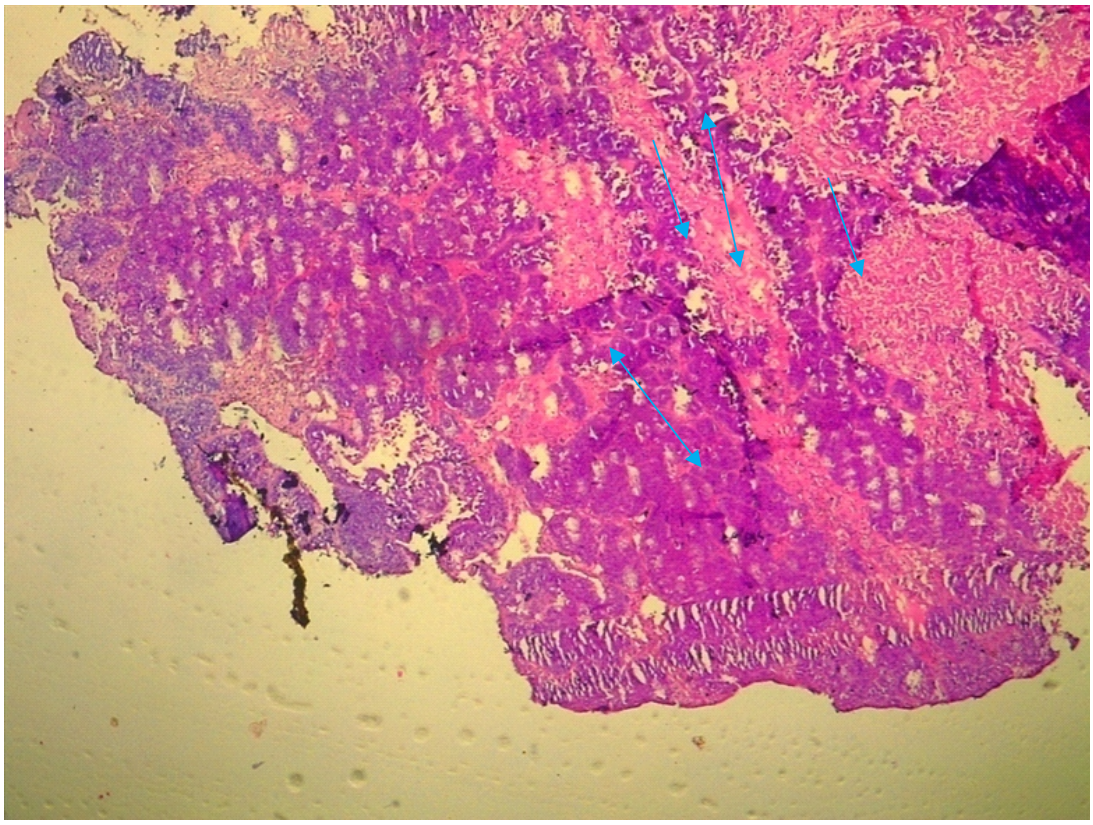

Figure 3: (hematoxylin /eosin, 40X)
Photomicrograph of nodule at low magnification showing total effacement of native nodule architecture by a tumour disposed in solid nests and trabecular pattern (double arrows) and areas of necrosis (single arrows).

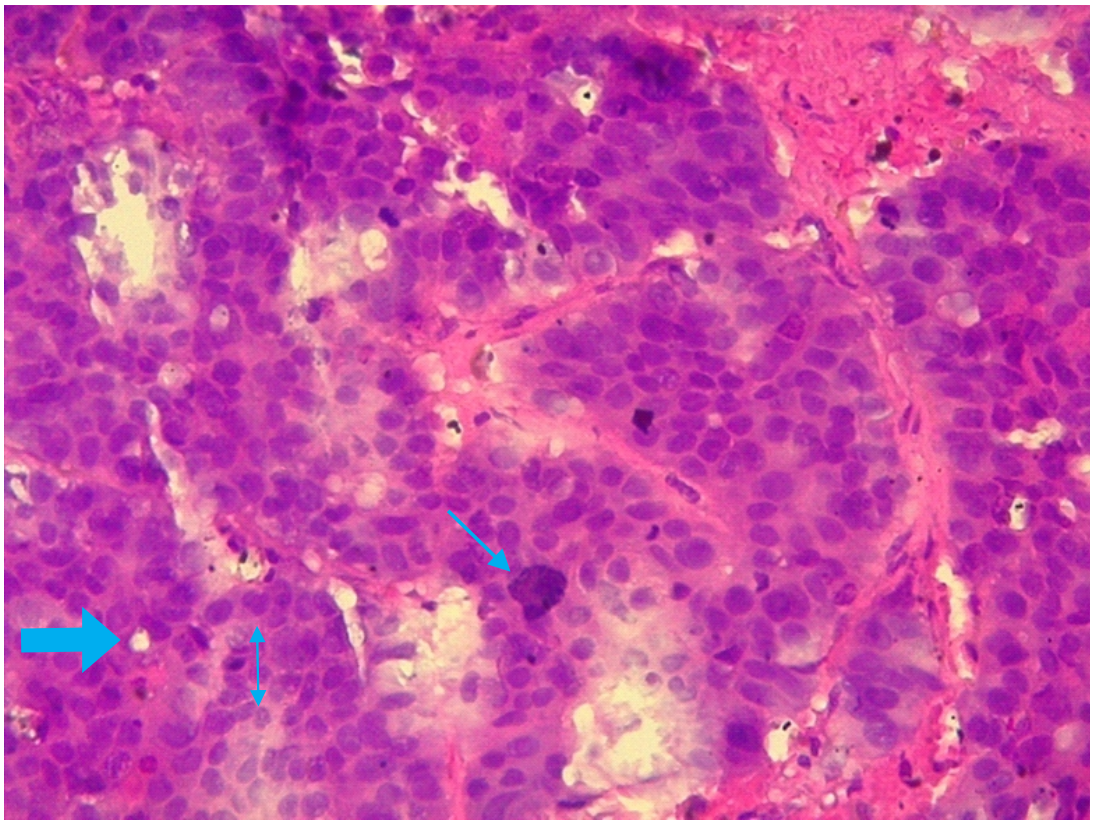

Figure 4: (hematoxylin/eosin, 400X)
Photomicrograph showing the solid nests separated by scanty fibrous septae composed of fairly uniform round to oval cells with indistinct borders having dark nuclei with dispersed chromatin giving a "salt & pepper" appearance in areas (double arrow). Mitotic figures (single arrows) and pseudorosettes (thick arrows) are noted.

Diagnostic tests aimed at identifying the primary site of the tumour, such as immunohistochemistry, thoraco-abdominal CT-Scan amongst others, could not be done due to financial constraints coupled with her poor state of health. She died on the 18th day of admission from disease progression.

DISCUSSION

Neuroendocrine neoplasms are an uncommon surgical disease globally that originate from neuroendocrine cells found in most body tissues. Malignant neuroendocrine neoplasms constitute 46.9% of all cases of neuroendocrine diseases.[6] They have no sex predilection and are commoner in the older age groups as in our index patient.

The usual primary sites of neuroendocrine neoplasms include the gastrointestinal tract and the Broncho-pulmonary tree, with areas of metastatic spread being the lymph nodes, liver, lungs, and occasionally the peritoneum.[6,7] The majority of the symptoms and signs of neuroendocrine neoplasms are non-specific and take a protracted course. Skin metastasis is infrequent in clinical practice.

Carcinomas of the breast, uterus, colon, lungs, stomach, and kidney, and melanoma most frequently produce skin metastasis. Skin metastasis depicts a poor prognosis with associated high mortality and has been reported in approximately 9% of patients with metastatic cancer, while other studies showed 3-4%.[8]

Skin metastasis from neuroendocrine neoplasms is extremely infrequent, with few reported cases in the literature among Caucasians as against Africans or people of African descent, in whom the incidence of the disease is considered higher.[9] Secondaries to the skin from malignant neuroendocrine neoplasms commonly manifest as nodular swellings of varying colours and sizes, however, with no site predilection as was the case in our patient.

Amongst the patients who developed skin metastasis, most of them developed skin metastasis long after the systemic manifestation of the disease. This is similar to our index patient but at variance with a report of Mahmut et al.,[10] where the skin nodules preceded the systemic symptoms.

Jaroslaw et al.,[3] in their series, reported the presence of a single nodule in their patients with no evidence of visceral metastasis. Their patients were followed up for a minimum of 36 months after diagnosis. This is in contrast to our patient with multiple nodules and visceral and bone metastasis, which suggests a terminal stage of the disease, thus accounting for her early demise.

Merkel cell carcinoma is top among the differential diagnoses of skin metastasis from malignant neuroendocrine neoplasms. It is a rare primary cutaneous neuroendocrine neoplasm with a predilection for sun-exposed parts of the body, such as the face and neck. Peculiar to this lesion is the presence of a higher mitotic rate, positive staining for CK 20, and the systemic symptoms preceded by the skin lesions.[9]

Due to the infrequent occurrence of neuroendocrine neoplasms, arriving at a definitive diagnosis is usually challenging, with most patients being diagnosed later in the disease. However, in patients with skin nodules, as in our case, the diagnosis was expedited following the histology of the lesion despite her late presentation.

The diagnosis of neuroendocrine tumours involves clinical, biochemical, radiological and histological assessments. Biochemical analysis of blood samples has greatly contributed to the diagnostic work-up of patients with neuroendocrine tumours. Due to its primary expression throughout the neuroendocrine system, Chromogranin A is a widely accepted biomarker for neuroendocrine tumours. It has also been traditionally used in the management of patients with tumours of gastro-enteropancreatic origin.

Diagnostic imaging utilized in patients with neuroendocrine neoplasms includes computed tomography (CT) scan, magnetic resonance imaging (MRI), somatostatin-analogue-based imaging modalities, and endoscopy, depending on the suspected primary tumour site and its extent.[3] MRI is of great value due to better soft tissue delineation than a CT scan and can detect lesions, especially hepatic deposits, that CT scans frequently miss. The role of conventional ultrasonography scans is for the assessment of visceral deposits. The intra-operative tool of choice is to localize liver deposits for ablation or examine the pancreas for small undetectable

tumours on a CT scan or MRI. Our patient could not carry out the above investigations except abdominopelvic USS due to financial constraints.

Carcinoma of unknown primary constitutes 2.3-4.2% of all Malignancies. The localization of the primary site in metastatic NETs remains a challenge despite advances in diagnostic modalities. Gustavo et al.[1] could not unravel the primary site in their report despite having their patient scanned with CT and Scintigraphy. However, recent evidence suggests the benefits of endoscopic USS and PET-CT scans.

The management of malignant neuroendocrine neoplasm is multidisciplinary, multimodal, and individualized. It depends on the site, extent, performance status, and the presence of co-morbidity. Such treatments are tailored based on the intent of management, whether curative or palliative. The various modalities utilized include surgical resection, somatostatin analogues, cytotoxics, and targeted therapy.[3,6]

The World Health Organization in 2010 classified neuroendocrine neoplasms into well-differentiated and poorly differentiated tumours based on mitotic index and K1- 67 proliferation index, with the extent of differentiation as a strong prognostic factor.[11] Michael et al.[12,] in their report, showed that hepatic metastasis was a poor prognostic factor. Other poor prognostic factors include lymphovascular invasion, extensive necrosis, high mitotic index, and high-grade cellular atypia. Poorly differentiated NETs with Ki 67> 20% carry the worst prognosis.[1] The patient herein, in addition to having skin and hepatic metastasis, also had bony metastasis with eye involvement, implying an incurable stage of the disease, thus necessitating palliative care prior to her demise from the progression of the disease.

This study was limited as it lacked scientific rigor, especially as it did not assess some biochemical parameters identified as biomarkers of NETs. In addition, imaging for localization of the primary site of the tumour was not done due to financial constraints.

CONCLUSION

Skin metastasis from malignant neuroendocrine neoplasms is rare globally and extremely rare among native Black Africans. This case highlights an aggressive disease with skin, visceral, and bony involvement, indicating a poor prognostic outcome. Therefore, a high index of suspicion is needed to avert delayed diagnosis with its attendant consequences, especially in resource–limited settings.

REFERENCES

1. Gustavo MA, Danielle Q, Tullia C, Rosangela R, Marcia R. Cutaneous Metastasis of Neuroendocrine Carcinoma with Unknown Primary Site: Case Report and Review of the Literature. Case Rep Dermatol. 2015;7(3): 263-274
2. Monica V, Luigi R, Silverio T, Maria C, Patrizia V, Federica T. Metachronous and Synchronous Cancers in patients with neuroendocrine tumours. Oncology. 2020;98(1):10-15
3. Jedrych J, Basam K, Klenistra DS, Pulitzer M. Cutaneous metastasis as an initial manifestation of visceral well-differentiated neuroendocrine tumour; a report of four cases and a review of literature. J Cutan Pathol. 2014; 41:113-122
4. Andres GB, Steven MM, Sirunya S. Metastatic neuroendocrine carcinoma in the skin. DOJ .2017;23(1):8
5. Guo LJ, Tang CW. Somatostatin analogues do not prevent carcinoid crises. Asian Pac J Cancer Prev. 2014;15 (16):6679-6683.
6. Darba J, Marsa A. Exploring the current status of neuroendocrine tumours; a population-based analysis of epidemiology, management, and use of resources. BMC Cancer. 2019; 19: 1226.
7. Salyers WJ, Vega KJ, Munoz JC, Trotman BW, Tanev SS. Neuroendocrine tumours of the gastrointestinal tract; Case reports and literature review. World J Gastrointest Oncol. 2014; 6:301-310.
8. Raffaella G, Ivana P, Alessw R, Cristina C, Dorotea S, Dario G. A Rare Case of a Young Patient with NET: Cutaneous Metastasis Represents Optimal Target to Monitor the Benefit of a Treatment. Ann Case Report.2020;14:299

9. Chan S, Dian G, Shouhao Z, Ying X. Racial Differences in the incidence and survival of patients with Neuroendocrine tumours. Pancreas. 48(19): 1373-1379.

10. Mahmut E, Ceren B, Esra A. Cutaneous Nodules as an initial manifestation of Neuroendocrine Carcinoma with Unknown Primary Site. A Case Report. J Turk Acad Dermatol. 2021; 15(3):80-82.

11. Oana P, Sorina M, Stelian P, Andrei D, Robert A, Marioara C, Anca A et al. The new WHO classification of gastrointestinal neuroendocrine tumours and immunohistochemical expression of somatostatin receptors 2 and 5. Exp Ther Med.2021; 22(4):1179.

12. Michael J, David L, Calvin L. Simron S. Principles of diagnosis and management of neuroendocrine tumours. CMAJ. 2017; 189(10):398-404.