

## Case Report

### A Rare Case of a Young Patients with NET: Cutaneous Metastases Represent Optimal Targets to Monitor the Benefit of a Treatment

Raffaella Giuffrida<sup>1\*</sup>, Ivana Puliafito<sup>2</sup>, Alessio Russo<sup>3</sup>, Cristina Colarossi<sup>4</sup>, Dorotea Sciacca<sup>2</sup>, Dario Giuffrida<sup>2</sup>

<sup>1</sup>Cell and Molecular Biology Unit, IOM Ricerca Srl, Italy

<sup>2</sup>Oncology Unit, Mediterranean Institute of Oncology, Italy

<sup>3</sup>Radiology Unit, Mediterranean Institute of Oncology, Italy

<sup>4</sup>Pathology Unit, Mediterranean Institute of Oncology, Italy

\***Corresponding author:** Raffaella Giuffrida, Cell and Molecular Biology Unit, IOM Ricerca Srl, 11 Penninazzo Street, Viagrande, I-95029 Catania, Italy. Tel: +39 95 7924711; +39 392 8871065; Email: raffaella.giuffrida@grupposamed.com

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#### Abstract

Neuroendocrine Tumors (NETs) are considered rare malignancies that are increasingly becoming more recognized. NETs can occur throughout the body developing from cells of the neuroendocrine system that is found in organs such as lungs and gastrointestinal tract, they can produce a variety of hormones. Gastrointestinal NETs often metastasize to lymph nodes and liver but rarely can involve the skin where they appear as firm nodes. The presence of cutaneous lesions is often associated with high morbidity and mortality. We report a rare case of a patient with skin metastases from NET. Our patient was a 30-year-old white female who initially presented abdominal pain, nausea, vomiting and diarrhoea, and later was diagnosed with gastrointestinal-NET. Whole body CT-scan showed several hepatic metastases and thoracic and pleural node metastases. Moreover, at diagnosis, patient presented scattered cutaneous nodes on the chest. Our patient showed a decrease of the skin lesions as soon as she got a benefit from the therapy. In clinical practice, cutaneous metastases from NETs are rare and correlate with poor prognosis. In our report, cutaneous lesions represent optimal targets to monitor the benefit of a treatment.

**Keywords:** Metastases; Neuroendocrine-Tumor; Skin; Target; Treatment

#### Introduction

Neuroendocrine Tumors (NETs) are a heterogeneous group of neoplasms arising from the neuroendocrine system. They are composed by cells possessing both nerve and endocrine cell features. Neuroendocrine tumors may arise in the gastro-intestinal tract, ovaries, lungs and thymus. NETs may present with a wide variety of functional and non-functional endocrine syndromes, may be familial and have other associated tumors. Liver, bones and lymphnodes are common sites for metastatic disease. A rarer site of metastases of NET is the skin. We report the case of a patient with skin metastases from NET and review literature.

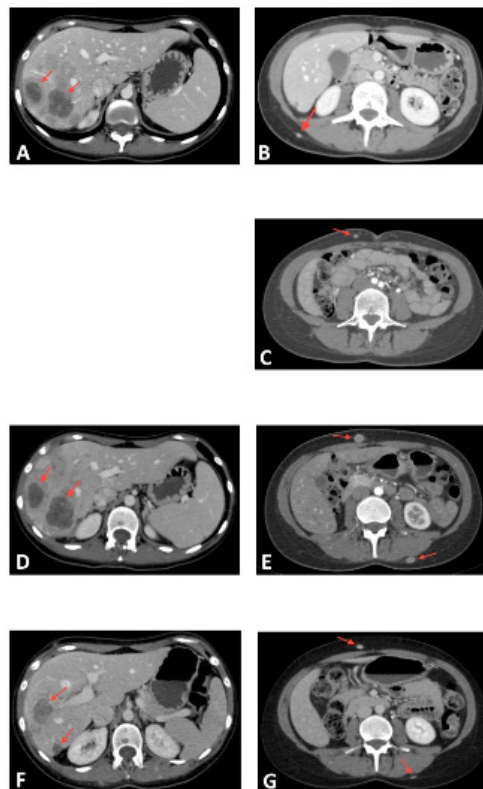
#### Case Report

We report a case of a 30-year-old white female with no co-morbidities, who arrived at our institution in January 2017, presenting abdominal pain, nausea, vomiting and diarrhea. Abdominal ultrasound showed two hepatic lesions of 10 and 4.6 cm in VI and VII hepatic segments, respectively. Abdomen CT-scan confirmed several hepatic metastases. At diagnosis, patient presented also cutaneous nodes, mainly localized on the right and left breast, on the left supraclavicular region and in paravertebral subcutaneous region. Hepatic biopsy was performed, with diagnosis of neuroendocrine tumor. On the basis of immunohistochemical stains, positive for cytokeratin AE 1/3, Synaptophysin, Chromogranin and CDX2, and negative for Cytokeratin 7 and 20, Thyroid Transcription Factor 1 (TTF-1),

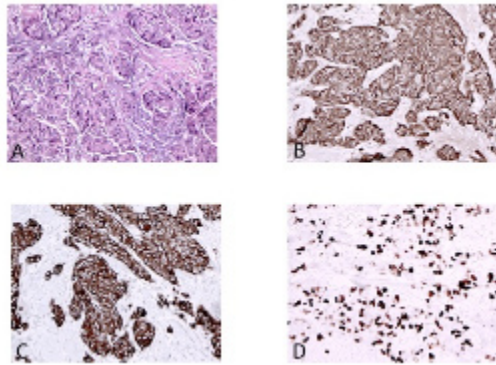
S100, Vimentin, Leukocyte Common Antigen (LCA), and on the basis of Ki-67 expression (45%), NET was classified as Grade 3 (G3). Primary cancer was not found. On March 2017 patient repeated a whole body CT-scan showing liver metastases, cutaneous thoracic nodes metastases, pleural node of 24 mm and supraclavicular nodes (Figure 1A and B).

A new biopsy of right cervical lymph node was performed. Diagnosis was poorly differentiated neuroendocrine carcinoma with intermediate and large cell types. Ki-67 expression was 40% and chromogranin A was > 700 ng/L (0-100). Endoscopy was negative. From March to July 2017, patient received 6 cycles of chemotherapy with cis-Platinum and Etoposide obtaining a partial response with disappearance of skin lesions. In November 2017 patient performed a whole body CT-scan showing the appearance of brain metastases, successively confirmed by NMR. Whole brain radiotherapy with conventional dose was administrated, subsequently the patient begun new chemotherapeutic treatment with Temozolamide and Capecitabine. In May 2018, after 3 cycles of treatment, new diffuse cutaneous nodes appeared all over the torax (Figure 1C). In June 2018 a new biopsy of skin metastases was performed and the pathology report was poorly differentiated Neuroendocrine Tumor (NEC G3), on the basis of haematoxylin/eosin and immunohistochemical stainings (Figure 2A).

Indeed, bioptic samples resulted positive for Chromogranin A and Synaptophysin, and Ki-67 was 40% (Figure 2 B-D). In order to eventually subject the patient to an immunotherapy or biological treatment, we also evaluated the mutational state of MET and genes involved in Mismatch Repair System (MLH1, MSH2, MSH6 and PMS2). No mutation was found. In July 2018 we started treatment with FOLFIRI. In October 2018 new cutaneous nodes were detected (Figure 1E). Whole body CT scan showed Stable Disease (SD) in lung lesions, while liver metastases increased in size and number (Figure 1D). Only MRI showed downsizing of brain metastases. From November 2018, FOLFOX chemotherapy was administrated without appearance of new skin lesions, on the contrary, those lesions already existing appeared reduced in size, as well as hepatic lesions (Figure 1 F and G). In January 2019 no new skin lesions were present. Additionally, a further decrease of the skin lesions was observed at subsequent checks made in April and October 2019. Currently, the patient is still subjected to FOLFOX chemotherapy, seen the good response attained, as also assessed by the cutaneous nodes reduction.



**Figure 1:** CT scan analysis, liver and cutaneous metastases are shown (red arrows) at diagnoses (A-B), during second line chemotherapy (C), during third line chemotherapy (D-E), during the last chemotherapy treatment (F-G).



**Figure 2:** (A) Hematoxylin and Eosin staining showing neuroendocrine carcinoma with trabecular and organoid pattern composed of cell of uniform size with round and oval nuclei, inconspicuous nucleoli, pyknotic nuclei and mitosis (magnification 20x). (B) Immunostaining showing diffuse and strong Chromogranin A expression (magnification 20x). (C) Immunostaining showing diffuse and strong Synaptophysin expression (magnification 20x). (D) Immunostaining showing a high Ki-67 expression that reflects high proliferative cell activity (magnification 20x).

## Discussion

Cutaneous metastases are uncommon in clinical practice. Melanoma, breast, stomach, lung, uterus, large intestine and kidney carcinomas are tumors that most frequently produce

cutaneous metastases. The appearance of skin metastasis result in a poor prognosis, their presence is often associated with high morbidity and mortality. Some studies report cutaneous metastasis in about 9% of patients with metastatic cancer, others in 3-4% [1]. Neuroendocrine Tumors (NETs) begins in the hormone-producing cells of the neuroendocrine system that is found in organs such as lungs and gastrointestinal tract. Cutaneous metastases are more frequent in Merkel Cell Carcinoma but they are very rare for other types of NET [2]. From 1960 to today, in literature are described 41 cases of NET with skin metastasis (Table 1). 22 out of 41 patients were male and median age was 59 years (range from 19 to 82 year). 11 out of 41 patients had lung cancer; 10 out of 41 were patients with gastrointestinal carcinoma; 6 out of 41 were patients with carcinoma of unknown primary origin.

In clinical practice cutaneous metastases represent a sign of poor prognosis, but they can be useful to observe the therapeutic efficacy of a treatment. In our case report patient skin lesions resulted reduced as soon as the therapy showed beneficial effects; whereas, when skin lesions increased in number and size we could hypothesize a progression of the disease, and this was confirmed by the CT-scan. Moreover, in a small number of NETs skin lesions can occur not as metastases but as form of cutaneous manifestations of paraneoplastic lesions [3]. Paraneoplastic skin syndromes in patients with NETs are even more rare than cutaneous metastases. Examples of paraneoplastic skin manifestations in patients with NETs are necrolytic migratory erythema, dermatomyositis, granulomatous eruption, nodular panniculitis [4-7].

Lesion location	Primary site	Age	Gender	First author	year
face, hands and feet	lung	35	M	Reingold [8]	1960
scalp and trunk	Unknown	62	M	Bean [9]	1968
abdomen and limbs	Pancreas	73	F	Colin-Jones [10]	1969
Trunk	Testicles	19	M	Sullivan [11]	1981
trunk and thighs	lung	68	F	Archer [12]	1985
trunk and thighs	Stomach	80	M	Rodriguez [13]	1992
diffusely on the body	larynx	63	F	Scmidt [14]	1994
umbilical scar	GI tract	62	F	Grunewald [15]	1996
Eyelid	GI tract	67	M	McCracken [16]	1996
scalp	larynx	72	F	Ereno [17]	1997
face	lung	71	M	De Argila [18]	1999
trunk	larynx	61	M	Ottinetti [19]	2003
periumbilical	Pancreas	34	F	Zhang [20]	2003

multiple	Rectum	69	M	Bell [21]	2005
breast	breast	76	F	Vidulich [22]	2007
dorsum	lung	60	M	Santi [23]	2008
scalp	uterus	31	F	Chung [24]	2008
scalp	Bladder	20	M	Lee [25]	2009
head, neck and trunk	larynx	82	M	Simpson [26]	2009
scalp	Lung	55	F	Bloch [27]	2010
right axilla	lung	50	F	Yu [28]	2010
right forearm, abdomen and back	Thyroid	79	F	Sanii [29]	2011
breast	breast	50	F	Boyd [30]	2012
face	GI tract	65	M	Fluehler [2]	2013
breast	lung	60	F	Yuan [31]	2014
scalp	lung	55	M	Ishida [32]	2014
scalp	GI tract	62	M	Wang [33]	2014
scalp	lung	50	F	Jedrych [34]	2014
scalp	lung	74	M	Jedrych [34]	2014
scalp	Pancreas	67	F	Jedrych [34]	2014
dorsum	GI tract	67	F	Jedrych [34]	2014
Unknown	Unknown	60	F	Miquelestorena – Standley [35]	2014
lower limb	Unknown	65	M	Amorim [36]	2015
left hip	Pancreas	60	M	Shin	2015
face	lung	55	M	Belli	2016
Unknown	Unknown	75	F	Garcia	2017
Unknown	Unknown	48	M	Cojocari	2017
diffusely	cervyx	45	F	Devnani	2018
diffusely	larynx	55	M	Sankar	2018
right flank	GI tract	69	F	Dhingra	2018
Unknown	Pancreas	67	F	Laschinger	2018

**Table 1:** Case of NET with cutaneous metastases reported in literature.

## Conclusion

Despite more frequent and advanced imaging and endoscopic evaluations, NETs are still a difficult diagnosis to make given the wide range of its clinical presentation. Cutaneous metastases occur rarely and are usually associated with high morbidity and mortality. Importantly, the detection of skin lesions can be correlated with the progression of the disease and with the efficacy of the treatment. Therefore, cutaneous lesions and their localization represent optimal targets to monitor the benefit of a treatment.

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