

Recurrence of retroperitoneal Merkel cell carcinoma

A case report



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BACKGROUND: *Merkel cell carcinoma (MCC) is a neuroendocrine malignant neoplasm that usually has its primary location on the skin. It often metastasizes to lymph nodes, liver, lungs, bones and brain. Actually there have been few cases of MCC of the retroperitoneal region without a primary skin lesion.*

CASE PRESENTATION: *Our case is a male of 55 year old who initially underwent a partial resection (R1) of a bulky pelvic mass; the histopathological analysis and the immunohistochemistry showed the presence of neuroendocrine Merkel cells. The patient underwent 6 cycles of postoperative chemotherapy (carbon platinum and etoposide) and adjuvant radiotherapy. Afterwards the patient underwent surgery again with the complete resection of the tumour.*

DISCUSSION: *The histopathological and immunohistochemistry analysis of the first and the second surgical samples confirmed the diagnosis of a retroperitoneal high-grade neuroendocrine carcinoma with a high mitosis index. The immunohistochemistry profile showed neoplastic cell with: CD 20+, synaptophysin +, TTF-1-, neurofilaments +, CK 7-, chromogranin, Ki67 90%. In the patient's medical history no skin localizations were mentioned.*

CONCLUSION: *The hypothesis of a MCC with a primary retroperitoneal localization has been strength by the histopathological and immunohistochemistry analysis of two intra-operative samples from two different surgical procedure and from the absence of either a primary skin location or of secondary recurrences. Is therefore reinforced the theory that from a cell into a retroperitoneal lymph node can arise a retroperitoneal mass originating a Merkel cell tumour.*

KEY WORDS: Chemotherapy, Cytoreductive Surgery, Merkel carcinoma, Retroperitoneal recurrence

Introduction

MCC has been described for the first time in 1972 by Cyril Toker, who identified it as a usually primary skin trabecular cancer.

It is a rare neuroendocrine tumour with high aggressiveness.

This kind of cancer undergoes frequently distant metastasis (liver 13%, lungs 10-23%, bones 10-15% and brain 18%¹) and it shows a high incidence of local recurrence. MCC occurs mostly in Caucasian men in between the age of 60-80 years old.

Primary skin lesions are more common in sun-exposed regions.

We analyzed a rare case of a 52 years old man, who came to our attention for a bowel subocclusion. He firstly underwent a retroperitoneal mass resection and later on, he underwent another surgical procedure for a local recurrence.

The histopathological assay resulted in a primitive retroperitoneal Merkel cell carcinoma.

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Case presentation

In April 2012 was admitted to our ward a Caucasian man of 52 years old suffering from a subocclusion due to a pelvic recurrence from a MCC.

The patient had underwent a retroperitoneal mass resection on May 2011, R1, with internal iliac artery binding, nephrectomy and ureterectomy, 12 months before at the urologic department of another hospital.

The pelvic mass was first diagnosed in March 2011 after the appearance of lower right leg's swelling and pain. For this reason the patient had underwent a US scan and afterward a CT scan, in which the retroperitoneal lesion was shown.

The histological report from the surgery piece showed a retroperitoneal undifferentiated MCC, completely infiltrating the ureteral wall.

Immunohistochemistry had shown that the neoplasm cells were chromogranin +, synaptophysin +, neurofilaments +, CK20 + ("dot-like"), TTF1-, CK7-.

The proliferation index, evaluated with Ki67 was 90%. Two months later the patient was administered with post surgery chemotherapy as the oncologists suggested. The drugs utilized were carbonplatin AUC5 and etoposide 100 mg/m².

The six cycles of chemotherapy ended at the end of September 2011 and afterwards a chest and abdominal CT scan was done in order to reevaluate the situation (Fig. 2).

Considering the rapid tumour growth, despite the chemotherapy treatment, the patient undergoes radical radiotherapy of the pelvic mass. Later on, almost one month after the chemotherapy the patient did 30 radiotherapy sessions with a single dose of 2 Gy fpr for a total dose of 60 Gy. A following CT scan showed a discrete lesion response to the radiotherapy.

A second line chemotherapy treatment with Taxol (weekly dose of 50 mg/mq) was started. Afterward the patient

was admitted to our ward for intestinal subocclusion and abdominal pain (Fig. 3). After many discussions, evaluating all the possible solutions in a multidisciplinary meeting, we decided for the surgery; the patient underwent a R1 surgical cytoreduction (Fig. 1).

A midline explorative laparotomy was done and a large mass has been found into the abdominal cavity. The lesion was infiltrating the ileum, the right colon, the hepatic flexure, the sigmoid colon and the parietal peritoneum in the right side. During the surgery was performed an "enbloc" removal of the tumour, which requi-



Fig. 1: Surgical specimen.



Fig. 2: PET-TC after the first chemotherapy cycle.



Fig. 3: Bowel sub occlusion due to retroperitoneal mass.

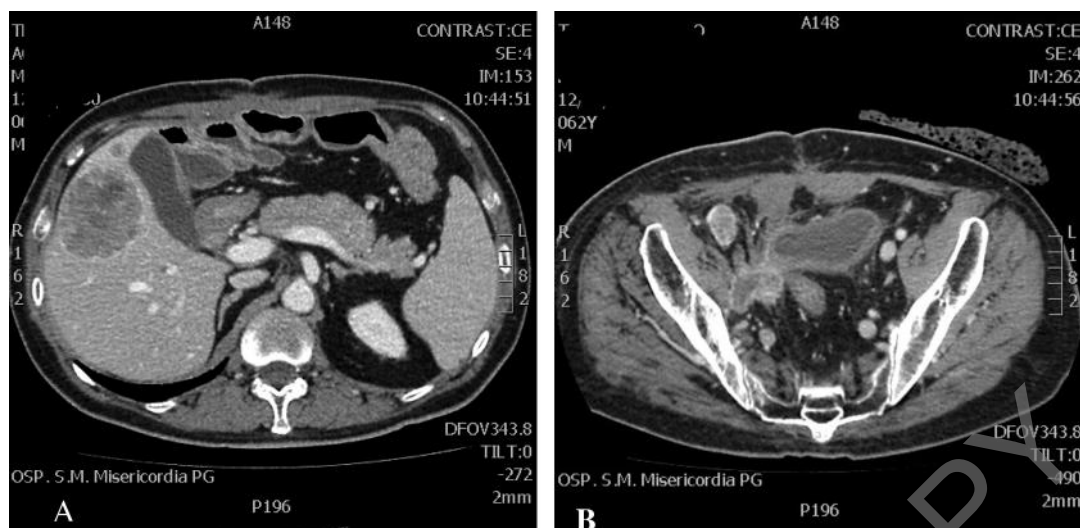


Fig. 4: A) Liver metastases
B) Retroperitoneal local recurrence.

red a right hemicolectomy extended to the transverse colon, resection of 30 cm of terminal ileum, omentectomy, wall peritonectomy in right side and resection of sigmoid colon; a terminal colostomy was done in accordance with Hartmann technique. The postoperative course was uneventful, that means without any medical and surgical complications.

The histological report of the second surgical specimen confirmed the previous diagnosis of neuroendocrine carcinoma of high degree of malignancy with a CD 20 + and Ki67 (clone MIB-1) 80%. Considering the mitotic index of the disease, colleagues from the oncology department have decided not to make Octreoscan to evaluate the possibility of using a radio metabolic therapy. The patient re-evaluated in the following months with CT scans showed further recurrence of pelvic mass with the addition of repetitive metastasis to the liver (Figs. 4a, 4b).

Discussion

Merkel cell carcinoma (MCC) is a rare and not so well studied carcinoma due to its recent discovered and its low incidence in the world. It seems to origin from a mechanoreceptor located in the basal layer of the epidermis 5.

However, in the recent time, with an implementation of literature data, Merkel cell cancer has been found in different locations such as the retroperitoneal area without an apparent primary skin site.

About its origin two main hypotheses have been made²⁻⁴: 1) the retroperitoneal mass originates from a retroperitoneal lymph node; 2) the primary skin lesion had spontaneously regressed by the time that the retroperitoneal mass was discovered.

The first hypothesis seems to be more consistent with the Merkel cell tumour characteristics; as a matter of

fact MCC is a highly aggressive tumour that metastasises in a short period of time.

According to the Italian Health Institute, the incidence of MCC between 1995 and 2006 was 0.14/100.00⁵ and the number is increasing due to the ageing population, the better diagnosis process and the increasing number of immunocompromised patients.

MCC generally occurs in elderly people with a ratio M/F of 1.6/1. The epidemiology mentioned above regards MCC with a primary skin lesion, because very little can be found on MCC with other origins in literature.

Histopathologically speaking MCC is a neuroendocrine tumour and numerous markers have been studied in order to make an immunohistochemistry diagnosis. Macroscopically it can appear in various forms such as trabecular, solid or locally diffused. Microscopically it has small blue cell, with "salt and pepper" chromatin pattern⁶.

Table I shows immunohistochemical markers in the differential diagnosis of MCC. Two main immunohistochemistry patterns were brought to light: the neuroendocrine and the epithelial one.

As regards to the epithelial pattern, MCC primarily expresses keratinous components with medium molecular weight as cytokeratins 8, 18, 19 and 20. The latter appears to be the most frequently expressed according to data reported by scientific literature.

The CD 20 is important in differential diagnosis, as other neuroendocrine tumours, such as small cell lung cancer, do not usually express it; this cytokeratin constitutes cytoskeleton's intermediate filaments of epithelial cells of the gastrointestinal tract, urinary tract and Merkel cells⁶. MCC also never expresses the marker TTF-1 (thyroid transcription factor 1), and this allows us to make differential diagnosis with small cell lung cancer, positive for CD 20.

As regards the neuroendocrine pattern, the main marker is the specific neuron enolase, presents in all tumours

TABLE I - *Immunohistochemical differential diagnosis (MCC:markel cell carcinoma; SCLC: small cell lung carcinoma; MM:malignant melanoma; LGNEC: low grade neuroendocrine carcinoma).*

	CK-20	TTF-1	NSE	S-100	GrA	SYP	NFP	CD56	MAP-2	LCA
MCC	+	-	+	-	+/-	+/-	+	+	+	-
SCLC	-	+	+/-	-	-/+	+	-/+	+	+	-
MM	-	-	-	+	-	-	+	-		
LGNEC	+	+	+	+	-/+					
Malignant Lymphoma	-	-	-	-	-	-/+	+			

TABLE II - *TNM classification*

Tumor (T)	
T1	≤ 2 cm tumor size
T2	> 2 cm but no more than 5 cm
T3	>5 cm
T4	invasion of bone, muscle, fascia or cartilage
Nodal (N)	
cN0	node negative by clinical exam (clinical or Imaging exam)
pN0	node negative by pathologic exam
N1	metastasis in regional node
N1a	micrometastasis (sentinel node or elective lymphadenectomy)
N1b	macrometastasis (clinically detectable, confirmed by surgery or fine-needle aspiration) in-transit metastasis
Metastasis (M)	
M0	no distant metastasis
M1	metastasis beyond regional lymph nodes
M1a	metastasis to skin, subcutaneous tissues or distant lymph nodes
M1b	metastasis to lung
M1c	metastasis to all other visceral sites

TABLE III

Stage				Five-year Survival (%)*
0	Tis	N0	M0	
IA	T1	pN0	M0	79
IB	T1	cN0	M0	60
IIA	T2/T3	pN0	M0	58
IIB	T2/T3	cN0	M0	49
IIC	T4	N0	M0	47
IIIA	Any T	N1a	M0	45
IIIB	Any T	N1b/N2	M0	30
IV	Any T	Any N	M1	18

of neuroendocrine origin; also CD 56 and adhesion molecules NCAM were mentioned, due to their co expression in both the neuroendocrine tumours of the respiratory tract and in MCC. Another typical marker of neuroendocrine tumours is Chromogranin A, which is expressed whenever there is soluble matrix of neurosecretory granules.

MCC tumours show a high percentage of positivity for this marker together with synaptophysin that instead can be positive even in non-MCC neuroendocrine tumours. The expression of the latter two markers also seems to be related to the aggressiveness of the tumour: high positivity for synaptophysin and CrA correlates with lower aggressiveness of the tumour.

New markers were also MCC tumour associated: microtubule's associated proteins MAPs. These appear to be specific for different cell types; for example Map2 seems to be expressed in tumours' Merkel cell even in the absence of positivity for CD20.

Concerning diagnosis and prognosis no studies have been done for MCC without a primary skin lesion; all the ones found in literature are data regarding MCC with primary skin lesion. However it is important to show TNM and stage classification proposed by Yiengpruksawan ⁶ (Table II and III).

During the years stage classification has changed introducing stage Ia and Ib according to a study did by Yiengpruksawan and Allen et al. 11-13.

Prognosis is not good: literature data show that two-year survival rate is 30-50% ^{6,7}. Up to 44% of the patients can develop a local recurrence 16-18

Lymph nodes metastases have been detected also without a detectable primary lesion. Moreover distant dissemination is not rare: up to 40-50% of the patients develop visceral metastases ^{8,9}.

Agelli and Clegg have done some studies in the USA's population and the 5-year survival in 1034 cases is 75%, 59%, and 25% for localized, regional, and distant MCC, respectively ⁸. Overall survival is indeed influenced by the stage of presentation of the tumor ⁸.

Moreover it seems that younger age, female sex and localized disease are positive predictors of survival ^{9,10}.

Conclusion

Surgery procedure remains the primary option for this rare neuroendocrine tumour's treatment. Utility of chemotherapy and radiotherapy is still to demonstrate, even though those are used for MCC treatment.

Our case supports the hypothesis that within the retro-

peritoneal abdominal lymphatic system can grow Merkel tumour cells as a primary localization and not as a metastases.

It is a rare tumour, in unusual localization, and no studies can help us in order to understand the best treatment procedure to improve survival and reduce local recurrence.

In our case it is clear how the surgery after chemotherapy and radiotherapy, with the en bloc resection of the mass does increase the patient overall survival.

Riassunto

INTRODUZIONE: Il carcinoma a cellule di Merkel è una neoplasia maligna a carattere neuroendocrino solitamente primitivo cutaneo che metastatizza frequentemente l'apparato linfonodale, il fegato, il polmone, le ossa e il cervello. Sono stati documentati rari casi di carcinoma a cellule di Merkel di origine retro peritoneale senza evidenza di lesione primitiva cutanea.

CASO CLINICO: Riportiamo il caso di un pz di sesso M di 55 anni sottoposto inizialmente a asportazione parziale (R1) di voluminosa lesione espansiva pelvica la cui analisi anatomopatologica e immunostochimica documentava presenza di cellule di carcinoma neuroendocrino (merkel cell); sottoposto a VI cicli di chemioterapia post-operatoria (carboplatino e etoposide) e successiva RT adiuvante. Il paziente è stato sottoposto a reintervento con asportazione della neoplasia.

DISCUSSIONE: L'analisi Anatomopatologica e immunostochimica del primo e del secondo pezzo operatorio confermano diagnosi di carcinoma neuroendocrino ad elevato grado di malignità, elevato indice mitotico, localizzazione retro peritoneale. Il profilo immunostochimico delle cellule neoplastiche risulta: CD 20+, sinaptosina +, TTF-1 -, neuro filamenti +, CK 7-, cromogranina, Ki67 90%. All'APR non risulta nessuna localizzazione cutanea di malattia.

CONCLUSIONI: La conferma dell'analisi dei pezzi operatorii prelevati in due distinti interventi chirurgici e l'assenza della sede primitiva cutanea ne di localizzazioni secondarie in altre sedi, rafforza l'ipotesi che si tratti di un carcinoma neuroendocrino ad elevato grado di malignità compatibile con il carcinoma a cellule di Merkel primitivo retroperitoneale. Si consolida quindi la teoria che attraverso la trasformazione maligna di precursori neoplastici all'interno di un linfonodo retro peritoneale si possa formare una massa retro peritoneale identificabile con carcinoma a cellule di Merkel.

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