

## CASE REPORTS

# Unusual association of Merkel-cell carcinoma and hepatocellular carcinoma in alcohol and hepatitis C virus-related cirrhosis: Casual or causal relation?

Luigi Addario<sup>1</sup>, Ahmed Hashim<sup>2</sup>, Marsilia G. Marino<sup>3</sup>, Emanuela Monti<sup>3</sup>, Giovanni Tritto\*<sup>4</sup>

<sup>1</sup>Hepatology Unit, A. Cardarelli Hospital, Napoli, Italy

<sup>2</sup>Gastroenterology Dept., Brighton & Sussex University Hospitals, Brighton, United Kingdom

<sup>3</sup>Clinical Pathology Unit, A. Cardarelli Hospital, Napoli, Italy

<sup>4</sup>Gastroenterology Dept., St Thomas's Hospital, London, United Kingdom

**Received:** August 3, 2017

**Accepted:** September 24, 2017

**Online Published:** October 10, 2017

**DOI:** 10.5430/crim.v4n4p24

**URL:** <https://doi.org/10.5430/crim.v4n4p24>

## ABSTRACT

**Background:** Merkel-cell carcinoma (MCC) is a rare and highly aggressive skin cancer. The estimated annual incidence rate of MCC is increasing, and the mortality rate is considerably higher worse than that of cutaneous melanoma. The risk of MCC is higher in immunosuppressed patients and in those with other malignancies.

**Case representation:** The present report is the first description of MCC associated with hepatocellular carcinoma in an immunocompetent patient with alcohol and hepatitis C virus (HCV)-related liver cirrhosis.

**Conclusions:** This case supports the hypothesis of HCV systemic oncogenicity, suggested by previous reports describing an association of this virus with lympho-proliferative disease, gastrointestinal, kidney, and breast malignancies, even though a causal relation or mechanism have not been clearly established. Further studies are needed to clarify whether the impairment of immune system associated with advanced cirrhosis may also play a role, by allowing opportunistic viruses to initiate oncogenic pathways. This paper finally highlights the importance of the screening for skin and systemic disorders in patients with chronic hepatitis C.

**Key Words:** Hepatitis C, Merkel cell carcinoma, Hepatocellular carcinoma, Cirrhosis

## 1. INTRODUCTION

Merkel-cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine tumour, first described in 1972.<sup>[1]</sup> Since its first description, more than 2,000 cases of MCC have been reported in the literature. The majority of the cases involve the head and neck regions, followed by limbs and trunk.<sup>[2]</sup> The reported annual incidence of MCC is 0.2-0.45 cases per 100,000 people, which is 100 times lower than melanoma.<sup>[3,4]</sup> However, the mortality rate of MCC is

33%,<sup>[5]</sup> which is significantly higher than that of melanoma.

Hepatitis C and liver cirrhosis have been linked to various cutaneous conditions, but the development of primary skin neoplasms in those patients has not been extensively described in the literature.

This report is the first description of an unusual association of MCC with hepatocellular carcinoma (HCC) in a patient with alcohol and hepatitis C virus (HCV)-related liver cirrhosis.

\*Correspondence: Giovanni Tritto; Email: [Giovanni.Tritto@nhs.net](mailto:Giovanni.Tritto@nhs.net); Address: Gastroenterology Dept., St Thomas's Hospital, Westminster Bridge Road, London SE17EH, United Kingdom.

## 2. CASE PRESENTATION

A 75-year-old farmer with a history of alcohol and HCV-related liver cirrhosis and HCC presented to hospital with a painful 40 mm round mass on the anter-tibial surface of his right lower limb (see Figure 1). The lesion had appeared six months earlier as a slowly growing, painless, firm, subcutaneous nodule, with no apparent epidermal involvement or skin ulceration, and was overlooked initially by the patient and his physician. Over the subsequent few months, the lesion attained a large diameter, leading the patient to be referred to the hospital for evaluation.



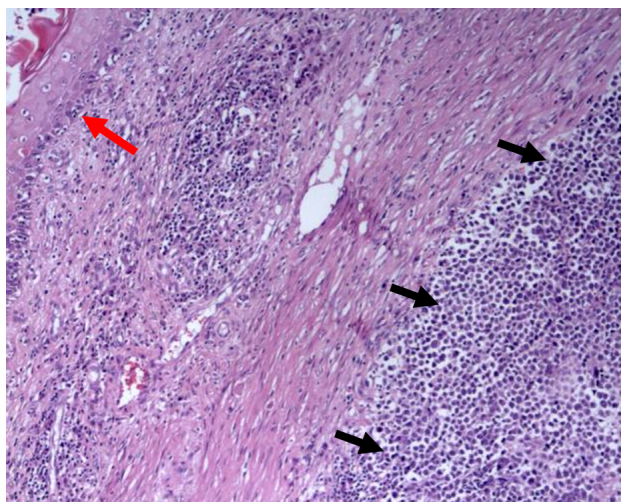
**Figure 1.** The merkel cell carcinoma lesion on the right leg of the patient

One year prior to this admission, the patient was diagnosed with monofocal hepatocellular carcinoma, 20 mm in diam-

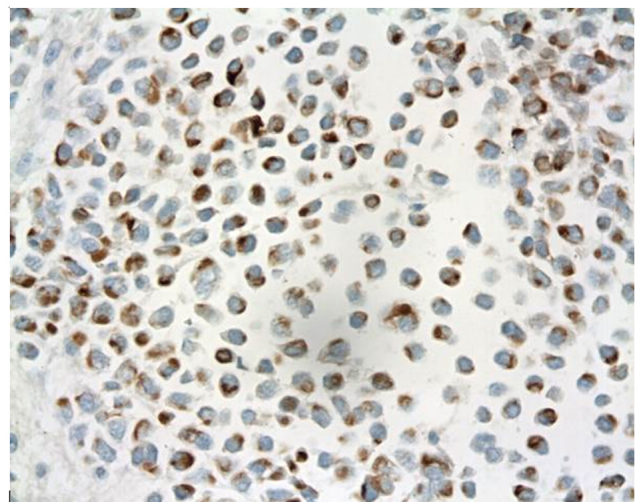
eter, in the fifth hepatic segment. The diagnosis was based on a typical enhancement pattern on triple-phase CT scan. Serum alpha feto protein (AFP) concentration was elevated at 110 ng/L. Oesophageal varices were identified at endoscopy, and his mild ascites was well controlled with diuretics. The patient declined loco-regional treatment for HCC, but remained abstinent from alcohol ever since.

On this admission, the patient showed no signs of liver decompensation. His Child-Pugh score was 7 (class B). Laboratory findings were as follows: haemoglobin 12.3 g/L, platelet count  $67 \times 10^9/L$ , ALT 55 IU/L, AST 61 IU/L, alkaline phosphatase 270 UI/L (normal range 40-130 UI/L), GGT 187 UI/L (normal range 10-71 UI/L), total bilirubin 2.1 mg/dl, albumin 30 g/L, INR 1.32. His hepatitis C RNA was positive, with genotype 2a/2c. AFP was 129 ng/ml. A chest and abdominal CT scan confirmed the single 25 mm HCC lesion in the 5th liver segment, with no other lesions elsewhere. His HIV test was negative.

The lower limb mass was surgically removed, and histopathology revealed a diagnosis of MCC (see Figure 2). Immunohistochemical staining showed strong positivity for CK20, a specific marker for MCC, and also for chromogranin, synaptophysin, and CD117. A staging CT did not show evidence of metastatic disease or enlargement of regional lymph nodes, and an octreotide scan did not reveal tumour spread. The patient refused local radiotherapy following excision of the MCC, and again declined radiofrequency ablation for his HCC.



A



B

**Figure 2.** A) Microscopic image of the MCC involving the deep dermis (lower right area of the slide, indicated by black arrows). The intact epidermis is visible in the top left corner (red arrow). B) Immunohistochemistry of MCC showing dotted immunoreactivity for cytokeratin.

Nine months later, the MCC recurred on an adjacent site on the same leg (see Figure 3), while an ultrasound scan revealed ascites and multifocal HCC lesions. AFP value was 540 ng/ml. The patient died three months later due to variceal bleeding and hepatic failure.



**Figure 3.** The recurrence of merkel cell carcinoma distal to the site of the excision of the previous lesion

### 3. DISCUSSION

The present report describes an unusual association of MCC with HCC in a farmer who is known to have alcohol and HCV-related cirrhosis. No similar cases have been reported to date in the literature in immunocompetent patients.

The development of MCC is linked to a polyomavirus, which is a non-enveloped, double-stranded DNA virus.<sup>[2,3]</sup> Due to its non-specific macroscopic characteristics, MCC cannot be diagnosed without the support of histopathological studies.<sup>[6]</sup> The treatment of choice for MCC is surgical excision with wide margins, and adjuvant radiotherapy when wide local excision cannot be achieved.<sup>[7]</sup> Since MCC is a neuroendocrine tumour, it demonstrates chemosensitivity to agents used in treating small-cell lung cancer, such as carboplatin, vincristine, and etoposide, but the role of chemotherapy is much less established than that of radiotherapy.<sup>[7,8]</sup>

Our patient was known to have chronic hepatitis C infection, which can induce malignant transformation. By far, the commonest malignant transformation in chronic hepatitis C patients is the development of HCC. Although the oncogenic activity of HCV toward HCC has been shown in many reports, the ability of HCV to promote other cancerous diseases is still under investigation through molecular and clinical research.<sup>[9-11]</sup> HCV chronic infection is associated with cancers of lymphohaemopoietic tissue involving, in particular, B-cells. The pathogenesis of HCV-induced lymphoma is not well understood, but one explanation is that HCV results in chronic antigen stimulation, which leads to B-cell expansion and eventually monoclonal proliferation.<sup>[10]</sup> Moreover, Bruno and colleagues<sup>[9]</sup> showed an increased incidence of other primary malignancies in patients affected

by chronic HCV infection and HCC. In their report, common associations, in addition to lympho-proliferative disease, were gastrointestinal, kidney, and breast malignancies. Some reports propose that HCC, regardless of the aetiology of the underlying liver disease, can be linked to the development of synchronous neoplasia. A recent study established this link and highlighted the importance of screening for synchronous neoplasms in patients with HCC using PET scans.<sup>[12]</sup> Nonetheless, there are no substantial or direct links between HCV infection, with or without HCC, and skin malignancies.

While the association of MCC with HCC and HCV illustrated in this case is unique, common aetiological risk factors may partly explain it. Serological studies suggest that the human polyomaviruses sub-clinically infect the general population with rates ranging from 35% to 90%.<sup>[13]</sup> However, significant disease is almost only observed in patients with an impaired immune system. In this case, the patient was affected by alcoholic and HCV cirrhosis, which is known to induce immune dysfunction and susceptibility to infections. It is possible that the combined effect of chronic HCV infection, liver cirrhosis, and the presence of a simultaneous malignant process in the form of HCC, had rendered the patient relatively immunocompromised and, hence, highly susceptible to the development of MCC.

Although the surgical treatment of this patient's MCC was incomplete because of disease-positive margins, he refused radiotherapy. A more aggressive approach, however, would not have affected his outcome, which was mainly driven by his liver disease and primary liver cancer.

The development of MCC in this case could be considered as a new dermatological finding in the spectrum of cutaneous manifestations related to HCV infection. Among these, the classical and most common is the skin vasculitis, caused by type 2 mixed cryoglobulinemia.<sup>[14]</sup> Albeit less frequent, other primary dermatological disorders have also been described in relation to chronic HCV infection. These include - but are not limited to- lichen planus, acral necrolytic erythema, sialadenitis, and Mooren's corneal ulceration.<sup>[15,16]</sup> Nonetheless, the occurrence of a skin malignancy as a direct dermatological manifestation of HCV is very unusual.

Finally, this case highlights the need to screen chronic hepatitis C patients for any discrete skin lesions, in order to allow early detection and treatment of skin malignancies. Particular attention should be given to those who have concomitant HCC or advanced cirrhosis.

### CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

**REFERENCES**

- [1] Tokar C. Trabecular carcinoma of the skin. *Arch Dermatol.* 1972; 105: 107-11. PMID:5009611 <https://doi.org/10.1001/archderm.1972.01620040075020>
- [2] Poulsen M. Merkel-cell carcinoma of the skin. *Lancet Oncol.* 2004; 5: 593-9. [https://doi.org/10.1016/S1470-2045\(04\)01593-1](https://doi.org/10.1016/S1470-2045(04)01593-1)
- [3] Hodgson NC. Merkel cell carcinoma: changing incidence trends. *J Surg Oncol.* 2005; 89: 1-4. PMID:15611998 <https://doi.org/10.1002/jso.20167>
- [4] Schrama D, Ugurel S, Becker JC. Merkel cell carcinoma: recent insights and new treatment options. *Curr Opin Oncol.* 2012; 24: 141-9. PMID:22234254 <https://doi.org/10.1097/CCO.0b013e32834fc9fe>
- [5] Beker JC. Merkel cell carcinoma. *Ann Oncol.* 2010; 21 (Suppl 7): vii 81-5. <https://doi.org/10.1093/annonc/mdq366>
- [6] Bickle K, Glass LF, Messina JL, et al. Merkel cell carcinoma: a clinical, histopathologic, and immunohistochemical review. *Semin Cutan Med Surg.* 2004; 23: 46-53. [https://doi.org/10.1016/S1085-5629\(03\)00087-7](https://doi.org/10.1016/S1085-5629(03)00087-7)
- [7] Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005; 23: 2300-9. PMID:15800320 <https://doi.org/10.1200/JCO.2005.02.329>
- [8] Eng TY, Boersma MG, Fuller CD, et al. A comprehensive review of the treatment of Merkel cell carcinoma. *Am J Clin Oncol.* 2007; 30: 624-36. PMID:18091058 <https://doi.org/10.1097/COC.0b013e318142c882>
- [9] Bruno G, Andreozzi P, Graf U, et al. Hepatitis C virus: a high risk factor for a second primary malignancy besides hepatocellular carcinoma. Fact or fiction? *Clin Ther.* 1999; 150: 413-8.
- [10] Rosa GD, Gobbo ML, Renzo AD, et al. High prevalence of hepatitis C virus infection in patients with B-cell lymphoproliferative disorders in Italy. *Am J Hematol.* 1997; 55: 77-82. [https://doi.org/10.1002/\(SICI\)1096-8652\(199706\)55:2<77::AID-AJH5>3.0.CO;2-#](https://doi.org/10.1002/(SICI)1096-8652(199706)55:2<77::AID-AJH5>3.0.CO;2-#)
- [11] Vlaar APJ, Rietdijk ST, Zeerleder SS, et al. Malignancies associated with chronic hepatitis C: Case report and review of the literature. *Neth J Med.* 2011 May; 69(5): 211-5. PMID:21646667
- [12] Hiraoka A, Hirooka M, Ochi H, et al. Importance of screening for synchronous malignant neoplasms in patients with hepatocellular carcinoma: impact of FDG PET/CT. *Liver Int.* 2013; 33: 1085-91. PMID:23601196 <https://doi.org/10.1111/liv.12161>
- [13] Dalianis T, Hirsch HH. Human polyomaviruses in disease and cancer. *Virology.* 2013; 437: 63-72. PMID:23357733 <https://doi.org/10.1016/j.virol.2012.12.015>
- [14] Charles ED, Dustin LB. Hepatitis C Virus-Induced Cryoglobulinemia. *Kidney International.* 2009; 76(8): 818-24. PMID:19606079 <https://doi.org/10.1038/ki.2009.247>
- [15] Jadali Z. Dermatologic manifestations of hepatitis C infection and the effect of interferon therapy: A literature review. *Arch Iran Med.* 2012; 15(1): 43-8. PMID:22208443
- [16] Raslan HMZ, Ezzat WM, ElHamid MFA, et al. Skin manifestations of chronic hepatitis C virus infection in Cairo, Egypt. *East Mediterr Health J.* 2009; 15(3): 692-700. PMID:19731785