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## Pancreatic metastasis from a Merkel cell carcinoma diagnosed by ultrasound-guided biopsy<sup>☆</sup>



### Metástasis pancreática de carcinoma de células de Merkel diagnosticada mediante biopsia guiada por ecoendoscopia

Merkel cell carcinoma, also known as trabecular carcinoma of the skin, cutaneous APUDoma, primary small cell carcinoma of the skin or cutaneous neuroendocrine carcinoma, is a rare, aggressive skin cancer with a marked tendency towards locoregional and distant recurrence. Few cases of pancreatic metastases from Merkel cell carcinoma have been reported in the literature. We present the case of a 75-year-old man who had been diagnosed and treated for localised Merkel cell carcinoma with pancreatic recurrence.

The patient had a history of high blood pressure and hypercholesterolaemia, and had been diagnosed with Merkel cell carcinoma localised in the right forearm that was treated with extensive surgical resection. Six months later, he presented local recurrence, for which he received treatment with surgery and adjuvant radiotherapy. A follow-up computed tomography (CT) scan performed 6 months later revealed right axillary lymphadenopathy and flattening of the D11 vertebral body, as well as a new 38-mm solid lesion at the level of the pancreatic tail. The patient was asymptomatic, and laboratory tests showed no alteration in liver function tests or pancreatic enzymes. In view of these findings, endoscopic ultrasound was requested, in which a 47-mm hypoechoic mass with poorly defined borders was detected in the pancreatic tail and fine needle biopsy was performed with a 22G ProCore biopsy needle (Cook Endoscopy Inc., Limerick, Ireland) (Fig. 1). The histopathology study was consistent with Merkel cell carcinoma, with expression of neuroendocrine markers (synaptophysin and chromogranin) and positive staining for cytokeratin 20 (CK20) (Fig. 2). After confirming disease progression, aspiration of the axillary lymphadenopathies was considered unnecessary and the patient commenced palliative chemotherapy with carboplatin-etoposide.

Merkel cell carcinoma originates in cells of the same name located in the epidermal basal layer, where they

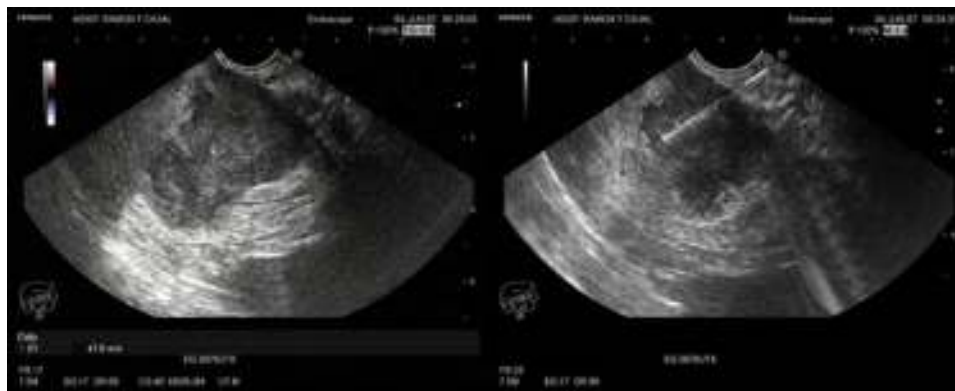
perform a mechanoreceptor function. Recent studies have shown that these tumour cells express epithelial markers such as CK20, which points to an origin in the epithelium rather than the neural crest, as previously thought.<sup>1</sup> It mainly affects Caucasian men older than 70 years,<sup>2</sup> and incidence is increasing due to population ageing. Onset has been related with exposure to both natural and artificial ultraviolet radiation, and also with immunosuppression, especially in HIV-positive patients,<sup>3</sup> solid organ transplant recipients<sup>4</sup> and patients with chronic lymphocytic leukaemia.<sup>5</sup> Merkel cell polyomavirus—a double-stranded DNA virus detected in up to 80% of cases—has recently been implicated in the pathogenesis of this tumour, although the prognostic implications of this finding are controversial.<sup>1</sup>

This type of carcinoma is most often found in sun-exposed areas, especially the head, neck and extremities, manifesting as a single, rapidly growing painless bluish-red nodule.<sup>6</sup> Almost half of patients (49%) present localised disease on diagnosis, and the presence of metastasis at presentation is rare (around 8%). However, the tumour is usually aggressive, with a 10-year survival of 57%.<sup>2</sup> It has a marked tendency towards local recurrence. Similarly, almost half of patients will develop distant metastases during the course of their disease, mainly bone and liver.<sup>2</sup> The occurrence of pancreatic metastases in Merkel cell carcinoma is exceptional, with only 14 cases having been published to date,<sup>7–9</sup> 4 of which were diagnosed by endoscopic ultrasound-guided fine needle aspiration cytology.<sup>9–11</sup>

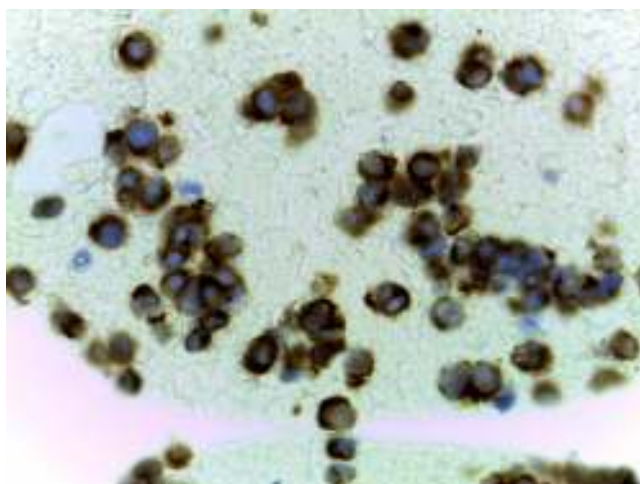
Treatment is usually extensive resection of the lesion in localised forms, combined with adjuvant radiotherapy if the resection is incomplete or there is a high risk of local recurrence. The current tendency is to biopsy the sentinel lymph node, and to perform dissection if lymph nodes are involved.<sup>12</sup> When distant disease appears, the prognosis worsens drastically, with a mean survival of 9 months. Chemotherapy regimens similar to those used in small cell lung carcinoma (with etoposide, cisplatin, vincristin, doxorubicin or cyclophosphamide) can be combined with radiotherapy or palliative surgery, although none of these strategies significantly increase survival.<sup>12</sup>

In the case presented, the distant disease in the pancreas appeared 1 year after the initial diagnosis, and the endoscopic ultrasound-guided biopsy was key in establishing the differential diagnosis with a possible primary tumour of the pancreatic gland. The therapeutic management of the patient was thus modified, avoiding unnecessary surgical resection. It should be borne in mind that metastases account for only 2% of all malignant lesions detected in the pancreas.<sup>13</sup> Furthermore, this is the first case of pancreatic metastasis from Merkel cell carcinoma diagnosed by endoscopic ultrasound and fine needle aspiration histocytology. The amount of material and type of sample that

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**Figure 1** Ultrasound image showing the hypoechoic pancreatic mass. The figure on the right shows insertion of the 22G ProCore biopsy needle.



**Figure 2** Histocytology image showing positive staining for CK20.

can be obtained with the new needles designed to obtain cytology and histology samples could theoretically aid in the diagnosis of particularly complex cases such as the one presented. This is because they obtain tissue cores that enable immunohistochemical studies to be performed and reduce the need for a cytopathologist in the endoscopy room during the procedure.<sup>14</sup> Both types of needles have been compared in the sampling of pancreatic lesions, presenting similar technical success and complication rates.<sup>15</sup>

In conclusion, metastases from Merkel cell carcinoma in the pancreas are rare, and endoscopic ultrasound is a crucial diagnostic tool in the differential diagnosis with other pancreatic tumours. The use of fine needles that can obtain both cytology and histology samples could improve the diagnostic yield of endoscopic ultrasound in certain cases that are difficult to classify using cytology alone.

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## Complete remission of Crohn's disease after high-dose alpha-interferon treatment for malignant melanoma<sup>☆</sup>



### Remisión completa de enfermedad de Crohn tras tratamiento con megadosis de interferón alfa por un melanoma maligno

Patients with inflammatory bowel disease (IBD), both ulcerative colitis (UC) and Crohn disease (CD), are at risk of developing nonmelanoma skin cancer, above all if they have taken or are currently taking thiopurine agents.<sup>1</sup> The association between IBD and melanoma was recently explored in an extensive meta-analysis of 12 studies with a total of 170 000 patients.<sup>2</sup> The authors concluded that, irrespective of the use of both thiopurine agents and anti-TNF, IBD increased the risk of melanoma, with a relative risk of 1.37 (95% CI 1.10–1.70).

Despite the considerable advances made in the treatment of melanoma following the introduction of antitarget drugs, such as vemurafenib, and immunomodulatory antibodies, such as ipilimumab and nivolumab, adjuvant treatment for high risk melanoma has not changed since the end of the 1990s. High-dose interferon (IFN) alfa 2b (IFN  $\alpha$ -2b), following the regimen used by Kirkwood et al.,<sup>3</sup> is the only therapy shown to prolong progression-free survival, although its benefit in terms of overall survival is less clear. The immunomodulatory effect of IFN on IBD is not fully understood.

We present the case of a woman of 42 years of age at the time of writing, a smoker of up to 0.5 pack-years, who had been diagnosed with perianal and ileocolic CD (A2L3pB1) at 27 years of age. She was initially treated with azathioprine and long-term corticosteroids, but made poor progress in terms of both gastrointestinal and general symptoms (arthralgia, asthenia, etc.). She was also given infliximab, which was withdrawn due to anaphylactic reaction, and adalimumab, which was withdrawn after 1 year due to a gradual loss of efficacy. Despite the therapy received, the perianal disease

worsened over time and the patient developed various pyogenic complications (fistulas and abscesses), undergoing up to 7 surgical procedures over the course of 4 years to drain the abscesses and to place setons in the fistula.

Ten years after the diagnosis of CD, the patient presented with a suspicious pigmented lesion on her left shoulder. Excisional biopsy revealed malignant nodular melanoma with microscopic ulceration and more than 6 mitoses/mm<sup>2</sup>. Breslow thickness was 3.4 mm (Clark stage III). An extension whole-body CT scan was performed, together with selective biopsy of 3 sentinel lymph nodes, which were negative on analysis. The patient was finally diagnosed with stage IIB melanoma (pT3bN0M0). Surgical treatment was completed with extended resection to include margins shown to be disease-free on histopathology. The patient was referred to the Medical Oncology Department where, in view of the ulceration and number of mitoses/mm<sup>2</sup> of the primary tumour, and despite the absence of nodal involvement, she was started on adjuvant treatment with high-dose IFN  $\alpha$ -2b, following the regimen proposed by Kirkwood et al. (15 million IU, 3 times/week for 48 weeks).<sup>3</sup> Before starting IFN treatment, the patient's quality of life was poor (up to 4 or 5 bowel movements per day, with severe asthenia, in addition to the perianal symptoms described above), and she was receiving 150 mg/day azathioprine, which was maintained during IFN therapy.

During IFN treatment, the patient presented mild toxicity (grade 1–2), which included influenza-like illness, asthenia, myalgia, headache, dysgeusia, nausea, enuresis and mild sensory neuropathy. These symptoms, however, did not require dose reduction, and the treatment was completed.

A few weeks after completion of IFN therapy, the patient reported improvement in her CD, and since then has only required 1 seton-placement procedure to manage her perianal disease. Her overall health is very good, with no gastrointestinal symptoms, and all immunosuppressants and immunomodulators given for CD have been discontinued. After 5 years of follow-up, she remains cancer-free.

Interferons are a group of antiviral molecules that were first introduced in clinical practice in 1957. Based on their receptor types on the cell membrane, IFNs are classified into type I and type II. IFN  $\alpha$  coding genes are located on human chromosome 9, and the protein has many different biological functions, including antiproliferative and immunomodulatory activities and potent antiviral activity.<sup>4</sup> IFN  $\alpha$  acts by regulating the expression of a wide range of genes involved in intracellular signalling pathways. After binding to its specific membrane receptor, IFN  $\alpha$  is thought to intervene in the regulation of over 300 genes and molecular pathways,

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