Merkel cell carcinoma with pleural effusion*

Derrame pleural por carcinoma de células de Merkel

To the Editor:

Merkel cell carcinoma (MCC) is a primary neuroendocrine tumor of the skin[1]. This is a rare but highly aggressive tumor, characterized by rapid growth and tendency to nodal and vascular invasion, locoregional recurrence, and metastasization[2]. However, pleural involvement is anecdotal and only three cases have been described in the literature[3–5]. To reach a diagnosis, a high clinical suspicion and immunohistochemical study of histological specimens are essential[3,4], given that it is a small cell neuroendocrine tumor that could be confused with other entities.

We report the case of a 69-year-old man who was admitted to our department with dyspnea and moderate pleural effusion. He was receiving immunosuppressive treatment after a kidney transplantation more than 10 years previously. One year before admission, an 8 mm papule was resected from the right side of the patient's forehead, diagnosed histologically as Merkel cell carcinoma. Subsequently, when the patient presented relapse in the right cervical lymph node, an extended resection was performed with node dissection followed by adjuvant radiation therapy. Extension studies conducted at the time of diagnosis and during follow-up showed no distant lesions. On admission, he had numerous raised, hypervascularized skin lesions measuring up to 2.5 cm, predominantly on his trunk (Fig. 1A). Thoracentesis yielded a very bloody fluid, with pH 6.93, LDH 3279 U/l, glucose <30 mg/dl, and CRP 9.5 mg/l. The cell count showed only red blood cells and atypical cell aggregates suspected of malignancy and no other common pleural fluid components were identified. A monomorphic population of small, round, blue cells with little cytoplasm and hyperchromatic nucleus with nuclear chromatin in salt and pepper were observed on histology (Fig. 1B). The immunohistochemical study showed synaptophysin and cytokeratin 20 (CK20) expression with a dot-like pattern in 100% of neoplastic cells, specific to MCC (Fig. 1C, D). Computed tomography showed a large anterior mediastinal mass with pleural and pericardial involvement, large retroperitoneal and mesenteric lymph node clusters, and bilateral perirenal implants.

MCC was first described in 1972 when Toker published a series of 5 elderly patients with skin tumors and extensive lymphatic involvement. The author highlighted the formation of trabeculae or cords with scant tumor cytoplasm as the main characteristic[1]. Electrodense granules and positivity to neuroendocrine and epithelial staining were subsequently detected on electron microscopy and immunohistochemistry, characteristics that are shared with Merkel cells of the skin, so the entity became known as MCC[3].

This is a rare tumor but one of the most aggressive, since up to one third of patients die as a result of the disease[6]. MCC usually affects elderly white patients, but has also been associated with immunosuppressive states, such as HIV infection, lymphoproliferative diseases, and solid organ transplantation[7]. Although it appears predominantly in photo-exposed areas, such as the head and neck, recent studies establish a relationship with Merkel polyomavirus in tumor carcinogenesis[8]. Incidence has increased in recent years, probably due to greater clinical knowledge, more precise methods for pathological diagnosis, aging of the population, and sun exposure[9]. In spite of its aggressiveness and its tendency to locoregional invasion and metastasization[7,10], only 3 cases with pleural involvement have been published in the literature[3–5].

The first, described by Watson in 1985, was a patient who, 20 years after resection of a skin tumor on his left hip, developed metastases and right pleural effusion. In this case, the diagnosis was only established from the cytological study of pleural fluid, since it resembled the histological samples obtained in the autopsy[3]. Years later, Payne et al.[4] published the case of a 77-year-old woman who had pleural effusion 1 year after resection of an MCC skin lesion. On this occasion, the authors only described the macroscopic characteristics of pleural fluid as bloody, and arrived at their diagnosis after cytological and immunohistochemical study of the cell block. The third case presented bilateral pleural effusion 2 years after resection of the primary skin lesion. In this case, histopathological and immunohistochemical studies of pleural biopsy led to diagnosis[5].

One novel aspect of our case is the description, for the first time in the literature, of the biochemical characteristics of the pleural fluid that demonstrate the enormous aggressiveness of the tumor. Decreased pH and glucose values in the pleura have been associated with a worse prognosis and more extensive pleural lesions[11]. In our case, these values were significantly reduced given the aggressiveness of the tumor and the extensive pleural involvement. This made it impossible to identify other common cellular components of pleural fluid, such as leukocytes or mesothelial cells, because they had been completely replaced by neoplastic cells.

In contrast to the cases published so far, our patient had been immunosuppressed for years since receiving a kidney transplant, so while both immunosuppressive treatment and solid organ transplantation have been described as risk factors for the development of this type of tumor[7], this immunosuppression could also have enhanced the enormous aggressiveness and rapid progress of the tumor.

Pleural MCC represents a diagnostic challenge due in part to its rarity and the fact that it is a tumor that can be confused with metastases from other tumors such as lymphoma, small cell carcinoma, melanoma, Ewing sarcoma, and neuroblastoma. In these cases, therefore, it is essential to maintain a high level of suspicion that so that the immunohistochemistry techniques necessary to establish its diagnosis can be performed. This tumor, due to its neuroendocrine origin, often expresses markers, such as CD56, chromogranin, or synaptophysin. For diagnosis, however, positivity for cytokeratin 20 with a perinuclear pattern is a highly sensitive and specific marker[12].

We believe that MCC may be a more frequent cause of malignant pleural effusion than currently recognized, and it may be responsible for pleural involvement even without evidence of skin lesions, given the descriptions published in the literature of cases of MCC with retroperitoneal or mediastinal involvement in which the primary tumor was not evident[13,14]. This highly aggressive and widely metastatic tumor may therefore not be recognized in the pleura unless the right immunohistochemical study to achieve a definitive diagnosis is conducted.

In conclusion, MCC is an entity that should be included in the differential diagnosis of malignant pleural effusion, especially in the case of small cell neuroendocrine tumors, even in the absence of skin lesions. In these cases, the determination of appropriate immunohistochemical markers will facilitate a definitive diagnosis.

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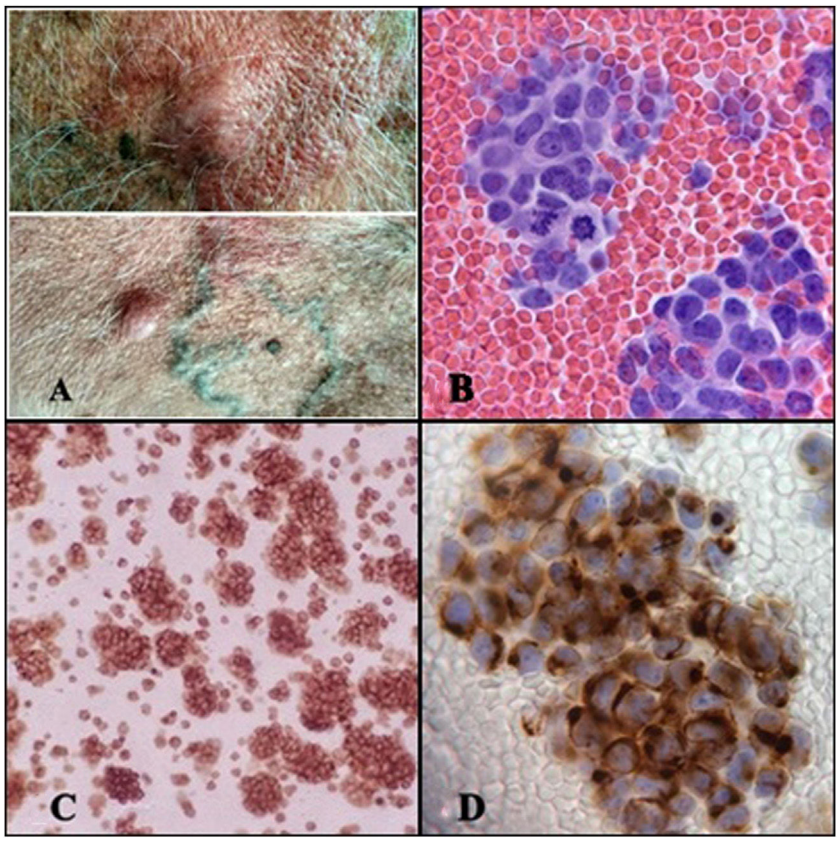

Fig. 1. A) Raised skin lesions on the anterior aspect of the trunk. B) Cytological study of pleural fluid showing a monomorphic cell population of small, round, blue cells with scant cytoplasm and chromatin in salt and pepper, with numerous cells in mitosis (H-E cell block, ·40). C) Immunohistochemical study with synaptophysin expression (neuroendocrine marker), showing fine dot-like granular paranuclear expression (SYN, ·20). D) Immunohistochemical study showing positive cytokeratin 20 with dot-like perinuclear staining pattern in all neoplastic cells, specific to Merkel cell carcinoma (CK-20, ·40).

Conflict of interests

The authors state that they have no conflict of interests.

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María J. Soler-Sempere[a,*], María O. Alvárez-Fernández[b], Isabel Padilla-Navas[a], María Cabezas-Macián[b], Jose F. Sánchez-Hernández[c], Eduardo García-Pachón[a]

[a] Sección de Neumología, Hospital General Universitario de Elche, Elche, Alicante, Spain
[b] Sección de Anatomía Patológica, Hospital General Universitario de Elche, Elche, Alicante, Spain
[c] Servicio de Análisis clínicos, Hospital General Universitario de Elche, Elche, Alicante, Spain

* Corresponding author.
E-mail address: majosoler1@hotmail.com (M.J. Soler-Sempere).

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Health Indicators in Hospitalized Patients With SARS-CoV-2 Pneumonia: A Comparison Between the First and Second Wave

Indicadores sanitarios en pacientes hospitalizados por neumonía SARS-COV-2: comparación entre la primera y segunda ola

Dear Editor,

The first cases of coronavirus disease 2019 (COVID-19) were identified in Wuhan, China[1] a year ago. However, few studies have been published comparing the characteristics and clinical outcomes of hospitalized patients with pneumonia secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of the first and second wave of the pandemic in Europe. Moreover, it has not been investigated whether patient management and health indicators improved during the second wave as a result of the experience acquired during the first. The objective of this study is to compare the characteristics and outcomes of hospitalized patients with COVID-19 of the first and second wave of the pandemic.

Data were collected from the medical reports of patients diagnosed with Covid-19 and admitted to our hospital, from February 2020 (date of first Covid-19 diagnosis) to December 31 (first wave until June 30; second wave since July 1). The study was approved by the Institutional Review Board (#2020/194). A case of Covid-19 was confirmed in the presence of a positive result in the reverse transcription polymerase chain reaction test on samples obtained from nasal or throat swabs, or a positive antigen test performed in accordance with the Spanish Ministry of Health recommendations.[2] Only laboratory-confirmed cases were considered for analysis. All patients diagnosed with Covid-19 pneumonia[3] were hospitalized and included in the study. All data were recorded at admission (+1 day). Patient were eligible for intensive care unit (ICU) admission if required mechanical ventilation or had a fraction of inspired oxygen (FiO_2) of at least 60% or more. Radiological anomalies were collected from reports of the Unit of Radiology.

We assumed missing data occurred at random depending on the clinical variables and performed multiple imputations using chained equations. Missing values were predicted from other outcome predictors. We created 100 datasets with identical known information but with differences in imputed values reflecting the uncertainty associated with imputations. In total <1% clinical data items were imputed (see Table 1). We used Chi-square test to compare proportions and Mann–Whitney *U* test for comparison of quantitative variables. Logistic regression analyses were performed to investigate the effects of the two waves on outcomes (risk of death, ICU admission and the risk for mechanical ventilation). For this purpose, regression models were tested using non-parametric techniques, adjusted for the predictors of the DALSH score (diabetes, age, lymphocytes, oxygen saturation, pH).[4] Results are presented as Odds Ratio (OR) with 95% confidence intervals (95%CI). Statistical analyses were carried out in R using the mice and mgcv packages. These packages are freely available at http://cran.r-project.org.

Fig. 1 shows the number of hospitalized patients by month during the two waves. Table 1 shows the characteristics of patients at baseline. As compared to the first wave, during the second wave, patients were significantly older, had fever less frequently, received the same medications and had similar comorbidities as patients of the first wave. Of note, the prevalence of heart failure was higher. Laboratory data show a lower inflammatory component (lower levels of lactate dehydrogenase and interleukin-6 and similar C-reactive protein levels) and lower concentrations of lymphocyte and platelets. In addition, respiratory distress (lower SaO_2, PaO_2/FiO_2 and SaO_2/FiO_2 ratios) and bilateral consolidations on chest X-ray were more frequent in the second wave, whereas interstitial abnormalities were less frequent. A higher use of corticosteroids and remdesivir was observed in the second wave, whereas hydroxychloroquine was hardly administered (5%) and Lopinavir/ritonavir were no longer used.

The median length of hospital stay was significantly higher during the first wave [10 (7, 19) vs 9 (6, 13) days; $P<.001$]. Health indicators were poorer in the first than in the second wave (admission to ICU, 13% vs 11%; mechanical ventilation, 11% vs 7%; deaths, 17% vs 15%).

After adjusting for diabetes, age, lymphocyte count, oxygen saturation and pH (DALSH score), the risk for mechanical ventilation (OR 0.45, 95%CI 0.26–0.79) and for death (OR 0.52, 95%CI 0.31–0.85) were significantly lower in the second wave than in the first wave. The risk of admission to ICU (0.65, 95%CI 0.40–1.05) was also lower but without reaching significantly statistical association.

According to the results obtained, the length of hospital stay, use of mechanical ventilation and mortality were lower in hospitalized patients with COVID-19 pneumonia during the second wave, as compared to the first. All despite the fact that patients in the second wave were older and their characteristics were associated with a higher risk for developing severe COVID-19 (lower SaO_2, PaO_2/FiO_2 and SaO_2/FiO_2 ratios).[5] These results persisted after adjustment for variables of severity (DALSH score).[4]

Previous studies with a different design also show that mortality decreased over time.[6,7] This cannot be attributed to demographic changes or variations in disease severity at presentation. Thus, whereas COVID-19 was approached as other severe respiratory diseases during the first wave, during the second wave the disease was managed based on the clinical experience acquired. As a result,

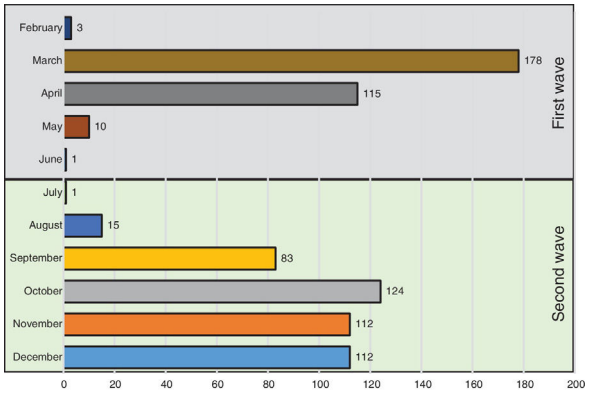

Fig. 1. Number of hospitalized patients by month during the two waves.