ORIGINAL ARTICLE

Primary Cutaneous Neuroendocrine Carcinoma, Merkel Cell Carcinoma. Case Series 1991–2012

Ramón Campillo, a Elisa Gil-Carcedo, b,* David Alonso, a Luis A. Vallejo, b Juan M. Oñate, c Luis M. Gil-Carcedo b

a Servicio de Cirugía Plástica, Hospital Universitario Rio Hortega, Universidad de Valladolid, Valladolid, Spain
b Servicio de Otorrinolaringología, Hospital Universitario Rio Hortega, Universidad de Valladolid, Valladolid, Spain
c Servicio de Anatomía Patológica, Hospital Universitario Rio Hortega, Universidad de Valladolid, Valladolid, Spain

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KEYWORDS
Carcinoma; Old age; Skin; Neuroendocrine; Immunohistochemistry; Surgery; Radiochemotherapy

Abstract
Introduction and objectives: Merkel cell carcinoma was first described by Toker in 1972. It is an uncommon, primary neuroendocrine skin carcinoma which appears in the dermoepidermic area, grows fast, is very aggressive and has a poor prognosis. The aim of this work is to highlight the importance of this tumour, which develops mainly in the skin of the head and neck area, and whose prevalence has increased in recent years.

Material and method: We gathered data on 16 patients suffering cutaneous neuroendocrine carcinoma treated at our hospital between September 12, 1991 and July 13, 2012. We indicated the age and gender of patients. We described the area where the tumour was located, indicating the size in millimetres, according to the major axis of the lesion.

Results: Most of the patients studied were over 70 years old, except for one who was 55. The highest frequency of cases appeared among patients aged over 80 years. In the cases studied, when the tumour appeared in the head and neck region (10/16), its location could be nasolateronasal, cheek-malar, upper eyelid, frontal or mandibular. The major axis of the lesion ranged between 7 and 35 mm. Unlike with epidermoid or basocellular carcinomas, recurrence and ganglionar metastases were common. Immunohistochemical (CK20) tests are essential for a correct diagnosis. Treatment is usually surgical and occasionally followed by radiotherapy and chemotherapy.

Conclusion: This carcinoma is not a very common skin tumour. It appears in old age, in the head and neck region in 50% of cases and often leads to exitus.

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* Corresponding author.
E-mail address: e.gilcarcedo@gmail.com (E. Gil-Carcedo).

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Primary Cutaneous Neuroendocrine Carcinoma

PALABRAS CLAVE
Carcinoma; Anciano; Piel; Neuroendocrino; Inmunohistoquímica; Cirugía; Radioquimioterapia

Carcinoma neuroendocrino primario de la piel, carcinoma de células de Merkel. Casuística 1991-2012

Resumen
Introducción y objetivos: El llamado clásicamente carcinoma de células de Merkel fue descrito por Toker en 1972, se trata de un carcinoma neuroendocrino primario de la piel. Aparece en la unión dermoepidérmica, es poco frecuente, de crecimiento rápido, agresivo y de mal pronóstico. El objetivo de este trabajo es dar a conocer este carcinoma que se implanta preferentemente en la piel de la cabeza y del cuello, y que aumenta su prevalencia en los últimos años.

Material y método: Recogemos 16 pacientes afectados por el carcinoma neuroendocrino primario de la piel, tratados en nuestro centro entre 12/09/91 y 13/07/12. Se precisa la edad y el sexo. Se describe la zona de implantación del tumor. Su tamaño lo expresamos en milímetros según el eje mayor de la lesión.

Resultados: Nuestros pacientes son mayores de 70 años, excepto la última incluida que contaba 55, la mayor frecuencia es en mayores de 80. Los casos recogidos, cuando asientan en la piel de cabeza y cuello (10/16) tienen localización: nasal-lateronasal, mejilla-malar, párpado superior, frontal, mandibular. El eje mayor de la lesión oscila entre 7 y 35 mm. A diferencia de lo que ocurre en los carcinomas espinocelulares o basocelulares son frecuentes las recurrencias y las metástasis. Para el diagnóstico es imprescindible la inmunohistoquímica con citoqueratina 20. El tratamiento es quirúrgico, ocasionalmente seguido de radioterapia y quimioterapia.

Conclusión: Se trata de un carcinoma poco frecuente de la piel, aparece en la edad avanzada, asienta en cabeza y cuello en más del 50% de los casos y conduce con frecuencia al exitus. © 2013 Elsevier España, S.L. Todos los derechos reservados.

Introduction
Merkel cell carcinoma was first described by Toker in 1972 when reporting 5 cases of elderly patients with solid tumours apparently derived from the dermis and hypodermis. When viewed under an optical microscope, their fundamental histo-architectural feature was seen to be the trabecular or string formation of cells with scant cytoplasm, for which reason it was referred to as cutaneous trabecular carcinoma. Toker initially assumed this tumour to be derived from undifferentiated eccrine gland cells.

When later studied under electron microscopy using immunohistochemistry techniques, the presence of electron-dense granules was detected, along with a positive response to neuroendocrine and epithelial staining, characteristics shared by Merkel cells, so it began to be referred to as a Merkel cell tumour.

In 1875, Sigmund Merkel detected clear oval cells on the dermoepidermal junction and these elements (which have since borne his name) are arranged to form an extensive axis at the level of the base layer, in close relation with melanocytes and nerve cells.

Although the exact origin and function of Merkel cells is still under investigation, they are thought to have characteristics of both epithelial and neuro-endocrine origin, and to arise from cells with the function of responding to mechanical pressure (mechanoreceptors). The most widely accepted hypothesis at the present time is that they originate on a common pluripotential precursor that gives rise to neuroendocrine and epithelial cells.

This carcinoma has received a number of names in the articles published in the literature: Toker’s tumour, cutaneous neoplasma of Merkel cells, cutaneous apudoma, neuroendocrine carcinoma of the skin, primitive carcinoma of small skin cells, primary undifferentiated carcinoma of the skin, cutaneous carcinoma of murky cells, primitive cutaneous carcinoma of small cells with endocrine differentiation and malignant trichodiscom.a We believe that the denomination best identifying its characteristics is that used in the title of this paper: primary cutaneous neuroendocrine carcinoma (PCNC).

This is a fast-growing carcinoma of the skin that appears on the dermo-epidermal junction. It is an infrequent, aggressive tumour with a poor prognosis and low survival rate, characterized by its relatively early tendency to invade lymph nodes and blood vessels, and by a high percentage of loco-regional recurrence in the year after surgical removal.

In a large percentage of PCNC cases, the existence of a mutation has been found, using molecular biology techniques, in the short arm of chromosome 10, which would bring about the inactivation of PTEN (a tumour suppressor gene).b

In 27% of cases, this malignant tumour is associated with the concomitant existence of other cutaneous neoplasias, such as Bowen’s carcinoma, basal cell carcinoma or epidermoid carcinoma. PCNC may appear together with lymphocytic leukaemia, B cell lymphoma or myeloma; and also in patients with immunological alterations, those subjected to organ transplants, or under prolonged treatment with immunosuppressant drugs.

PCNC habitually presents in Caucasian adults over 65 years of age, although cases have been reported in young patients carrying congenital ectodermal dysplasia syndrome. The advanced age of onset is related to the physiological reduction in both humoral and cellular immune function in elderly patients.
The lesions on the skin may be flat in appearance (plaque or papule) or raised (nodule), and are purplish-red in colour; they grow quickly and, as epidermal involvement is rare, they hardly ever cause ulcers. As in other skin tumours, a greater incidence has been reported in geographical regions with high indices of ultraviolet B radiation from sunlight. They tend to appear on areas exposed to the action of this radiation, so 55% are on the head and neck, 40% on the upper or lower limbs and the other 5% on the trunk.

Diagnosis in the pathology lab is complicated, as it may be easily confused with cutaneous metastases of other tumours such as Ewing’s sarcoma, neuroblastoma or, especially, “oat cell” carcinoma. A definitive diagnosis requires the use of electron microscopy (electrodense granules) or immunohistochemistry techniques using neuroendocrine and epithelial markers.

Despite being a rare entity, the incidence of PCNC has been increasing notably in recent years. This increase is undoubtedly real but the verification of the higher number of cases may also have been influenced by that fact that we now have better tools for recording cases, more accurate ways to diagnose it in the pathology lab, a better clinical understanding of PCNC and also an ageing population. Greater exposure to sunlight, an ever more frequent social custom, might also be at the root of this epidemiological increase.

Three of the points cited in this introduction justify the interest of this paper: the rise in the number of cases of this tumour, its greater severity compared to other epitheliomas and, fundamentally, the fact that it appears in the head and neck of over half the patients.

**Methods**

This is a retrospective analysis performed on the case histories of the 9 patients included in the study between 1991 and 2009, and the prospective monitoring of the 7 patients included from 2010 to 2012. For the selection of the retrospective cases, we used the archives of the Pathology Department and started the search from January 1st, 1991. The key words used for screening were: carcinoma, skin, neuroendocrine, Merkel, immunohistochemistry. Data acquisition was done by referring to the case histories computerized on the SICLINICA system.

Thus, we present here a total of 16 patients affected by PCNC and seen at our centre, the first on September 12th, 1991, and the last on July 13th, 2012. The age and gender of patients are noted. The area affected by the neoplasia is described, indicating those that appeared on the head and neck, and those starting elsewhere on the body. Within those on the head and neck, a reference is made to the specific area involved. The initial size of the lesion is expressed in millimetres for the longest axis reflected in the case file.

Since their appearance is not very well specified in the visual inspection, the pathology exam is used to provide the diagnosis. With haematoxilin-eosin, these carcinomas present a characteristic appearance of small bluish cells shared with other tumours such as small-cell lung carcinoma.

For this reason, it is fundamental to apply immunohistochemistry techniques, with cytokeratin 20 (CK20) staining being considered the gold standard. This technique, positive in 80%–90% of cases, confirms the diagnosis by presenting a characteristic paranuclear dot pattern, like a doughnut according to the English-language literature. Physiological Merkel cells on the skin share this positive response with tumoral cells, however, their paranuclear area will not stain but rather it will be distributed diffusely throughout the cytoplasm.

It is also essential to perform neuroendocrine staining to highlight this duality of their epithelial and neuroendocrine nature. In these cases, synaptophysin or chromogranin A is used as markers.

For the staging of the cases, we used the First Consensus Staging System of Lemos et al.

The existence or subsequent onset of loco-regional adenopathies or remote metastases is recorded. All patients were treated with surgery on one or more occasions. In some cases, supplementary radiation therapy and/or chemotherapy was applied. Particular emphasis was placed on investigating their progression towards exitus in an attempt to overcome the difficulties inherent to the specific features of these patients (age, residence in other provinces, intercurrent illnesses).

**Results**

The patients were over 70 years of age (15/16) except for the last one included, who was 55 (1/16). The greatest frequency is in those over 80 (10/16) (Fig. 1). In our series, PCNC is also somewhat more frequent among women (9/16) than among males (7/16). There is a notable increase in cases as years go by, as reflected in Fig. 2.

Four patients suffered from diabetes mellitus (4/16). Mention should be made of the greater aggressiveness of the tumour in one patient who presented, in addition to diabetes mellitus, advanced hepatitis due to virus c (1/16).

In 10/16 patients, the carcinoma was located on the skin of the head and neck (62.5%), namely nasal or lateronasal (4/10) (lateronasal is considered to be the inferior palpebral sulcus), cheek or malar (2/10), upper eyelid (2/10), forehead (1/10), jaw (1/10). In 6/16 cases (37.5%), it was located on the skin of other regions: upper limb (3/6), lower limb (2/6), shoulder (1/6). The largest of the carcinomas was the PCNC on the shoulder, at 120 mm. Considering those located in the head and neck, the larger axis of the lesion ranged between 7 and 35 mm, with an average of 14 mm.

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**Figure 1** Diagram showing that most of the 16 patients were over 80 years of age.
Figure 2  Distribution of cases between 1991 and 2012.

The appearance of the lesion is generally nodular and reddish in colour; although the skin surface of the mass is mostly smooth, it may be a little eroded or have scabby areas, although no clear ulceration is visible in any case (Fig. 3). A papillary form is less frequent (Fig. 4).

The pathology report referred to tumours made up of small round cells with an egg-shaped nucleus of disperse chromatin and scant cytoplasm, forming nests or trabeculae; mitoses and apoptotic bodies are notable (Fig. 5a). Diagnosis is provided through immunohistochemistry thanks to the use of CK20 as the main marker (Fig. 5b). In addition, the neuroendocrine markers mentioned in the Methods section are also used (Fig. 5c).

Applying the consensus reached by Lemos et al., the TNM staging of our cases distributes our patients over a similar frequency for stages i, iii and iv (at the moment of their diagnosis): 3 cases in stage i, 4 cases in stage iii and 3 cases in stage iv; no patient was included in stage ii.

All of the patients were treated surgically (16/16). With specific reference to those affecting the head and neck (10/16): 5 were treated solely with surgery, one of them for exclusively palliative purposes; in 5 cases, treatment was supplemented with radiation therapy and in one case combined with chemotherapy (carboplatin + etoposide).

The reconstruction phase was always straightforward due to the extreme looseness of the skin in the elderly. In all cases, simple techniques were used to repair the area: exeresis; direct closures or basic transfers and rotations. Myocutaneous flaps or microvascular free flaps were not necessary in any case.

Survival with head and neck tumours (10/16) was as follows: exitus in 6/10, alive with metastasis in PCNC 1/10. Alive and disease free 3/10, 2 of which were for less than 2 years (the 3 disease-free survival outcomes are for patients treated in 2008, 2011 and 2012. The patient alive with the disease had a tumour in the cheek and was subjected to exeresis of the tumour in November, 2011; in August, 2012, parotid and lymph node metastasis made it necessary to perform a parotidectomy and the removal of cervical and axillary lymph nodes, radiation therapy and chemotherapy (Fig. 4).

In all the cases of tumours not located on the head and neck (6/16), lymph node metastases made it necessary to remove the groin or axillary lymph nodes. Exitus occurred in 5 cases; the survivor was operated on for a carcinoma on the right wrist in May, 2011, an axillary lymphadenectomy was performed in September, 2011, due to lymph node metastasis and carboplatin + VP16 were applied.

Figure 3  Appearance of a PCNC on the nasal dorsum. Prior to exeresis (upper images) and 2 months after resection (lower images).
year, with an annual rise of 8%, and a rate of 0.6 per 100,000 inhabitants; cases have multiplied fourfold in the last 20 years. In Europe, the incidence per 100,000 inhabitants was 0.17 in 1993–1997 and 0.35 in 2003–2007. The Introduction section sets out the possible causes of this increase in case load.

Recent studies implicate Merkel cell polyomavirus in this carcinogenesis. This is a double-stranded DNA virus with 14 types, of which only 6 are detected in humans, and its role in carcinogenesis has been demonstrated in animal models. Molecular biology techniques using polymerase chain reaction (PCR) have enabled the presence of the virus to be studied in PCNCs. By characterization with PCR, viral DNA is known to exist in the primary tumour and in the metastases in 80% of cases and only in 16% of healthy tissue, in this latter case, with a viral load that is 60 times lower than that in tumorous cells.

Histologically, there are no differences between the tumour form associated with the virus and the form not associated with it (produced by accumulated genetic aberrations due to the influence of sunlight, immunosuppressorant treatments, etc.). Clinically, however, it has been possible to observe more aggressive behaviour in forms not associated with the virus, with a higher rate of relapses and lymph node involvement.

For this reason, with a view to clarifying the presence of the virus in the tumour, such diagnostic techniques as CM2B4 staining and monoclonal antibodies specifically targeting viral proteins are currently being developed.

The implication of a virus in tumorigenesis for this neoplasia opens up the door to a possible future treatment with specific anti-viral drugs.

In our patients, the macroscopic appearance of the lesions coincides with the descriptions given in the various reports in the literature (Figs. 3 and 4).

The location of the tumour’s appearance as cited in the literature (neck and head: 50%–55%; limbs: 40%; trunk: 5%–10%) differs from the distribution seen in our patients, where head and neck cases appear in 10/16 (62.5%) (Fig. 6). The male/female ratio cited is 2/1, whereas our PCNCs were somewhat more frequent in women (7 males/9 females). As with the published data, all our patients, except one, were over 70 years of age and most of them over 80 (Fig. 1). An immunodepressed status and HIV increase the risk of suffering from this carcinoma by a factor of 13, while the risk is 10 times higher in transplant recipients and in cases of chronic lymphoid leukaemia; among our cases, there is a significant number of patients with diabetes (25%).

Discussion

The increased incidence of PCNC seen at our hospital (Fig. 2) is similar to what happens in western countries. In the United States, recent studies show 1500 new cases appearing each year, with an annual rise of 8%, and a rate of 0.6 per 100,000 inhabitants; cases have multiplied fourfold in the last 20 years. In Europe, the incidence per 100,000 inhabitants was 0.17 in 1993–1997 and 0.35 in 2003–2007. The Introduction section sets out the possible causes of this increase in case load.

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Cases of spontaneous remission of the tumour (even with metastasis) have been reported after recovering a normal immunity profile. \(^{14}\)

Survival varies depending on the extension of the PCNC at the time of diagnosis: the 5-year survival rate is 64% when the tumour is exclusively local; 39% with adenopathies; 18% if there are remote metastases present. We are reflecting here the data of Lemos et al. \(^{13}\) but we feel that, in these age groups, it is difficult to measure survival over 5 years as the life expectancy is already low due to mere reasons of age.

As already mentioned, in tumours located in the head and neck, it was possible to confirm their evolution towards exitus reliably in 6/10 cases: all of them had suffered a relapse or metastasis, but the advanced age of the patients and the fact that many of them were resident in distant regions meant that in 2 cases it has not been possible to verify whether their demise was due solely and exclusively to the tumour or if other intercurrent illnesses were involved.

Histologically, PCNC is made up of small cells that are difficult to differentiate from those in other small round blue cell tumours: metastasis to the skin of small-cell lung carcinoma, cutaneous lymphoma, melanoma, Ewing’s sarcoma, neuroblastoma, rhabdomyosarcoma, basocellular carcinoma, undifferentiated epidermoid carcinoma. The cells making up the tumour in our cases have the characteristics described in the literature: they are small and round, with scant cytoplasm and an ovoid nucleus with disperse chromatina, forming characteristic nests or trabeculae, with numerous mitoses and apoptotic bodies (Fig. 5).

The definitive diagnosis is provided by immunohistochemistry, positive to CK20, as the paraocular staining has a characteristic dotted pattern; CK20 is negative for other small-cell carcinomas (Table 1). Kuwamoto \(^{16}\) and Rao et al. \(^{17}\) describe the pathology conditions necessary to consider a tumour as PCNC.

In the treatment of our patients, the surgical action seems to have been correct. This is not the case in the application of radiation therapy and chemotherapy that has to be more frequent (Table 2), with the proviso that the patient’s circumstances may or may not enable the accumulation of these therapeutic measures. The guidelines for handling these patients may possibly need to be corrected; this situation has been notified and discussed with the hospital’s oncology committee.

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Surgical treatment is fundamental. For safe surgery of the primitive tumour, it is necessary to leave a margin of at least 10 mm when the tumour measures less than 20 mm and a 20 mm margin when the tumour is larger than 20 mm. The neoplasia-free margins can be adjusted if suitable pathology support is available, using the Mohs surgery technique. In our cases, the reconstruction phase was carried out using local random or axial flaps and no microvascular free flaps were necessary.

Logically, it is necessary to eliminate cervical lymph nodes and/or regional lymphadenectomies in axilla or groin in N positive cases. \(^{3}\)

There are no definitive statistical data on action in N0 cases of PCNC. In the initial diagnostic biopsy, these tumours are mistakenly labelled as another type of skin tumour, with the result that, when they are N0, it is generally decided not to perform any prophylactic removal of cervical lymph nodes in the initial surgery (since it is not known that the tumour is so aggressive). The diagnosis of PCNC is obtained a posteriori by immunohistochemistry on the resection specimen; we stress that these cases had initially been considered as another kind of skin tumour following the pre-operative biopsy with no or very little lymphophilia and, for this reason (when they are N0), the cervical lymph nodes are not removed in the same surgery for the resection of the primitive tumour. A possible subsequent indication of cervical elimination once the definitive diagnosis of PCNC in situation N0 has been reached must be based on the stage of the tumour at the moment treatment is started.

For the decision on whether or not to perform lymph node surgery, and to specify the scope of the radiation therapy (either only on the bed of the primary tumour or also regional), it may be useful to study the sentinel lymph node. This technique was not used in any of our cases.

Local radiation therapy is necessary even in stage I as it reduces the risk of recurrence by a factor of 3.7. The current trend is to apply it in practically all PCNCs. It may not be necessary in tumours measuring less than 10 mm, with free surgical margins, in immunocompetent patients, with

### Table 1 Specificity of Immunohistochemistry for the Differential Diagnosis of Various Small-Cell Tumours.

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<thead>
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<th>Primary cutaneous neuroendocrine carcinoma</th>
<th>Small-cell lung carcinoma</th>
<th>Lymphoma</th>
<th>Melanoma</th>
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<tr>
<td>CK20</td>
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<tr>
<td>CK7</td>
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<td>S100</td>
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CK: cytokeratine; LCA: leucocyte common antigen; TTF: thyroid transcription factor.
Source: Rao et al. \(^{17}\)

### Table 2 Treatment Applied to Patients.

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<tr>
<td>Surgery (margin: 1–2 cm)</td>
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<tr>
<td>Re-intervention</td>
<td>4/16</td>
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<td>SLNB</td>
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<tr>
<td>Lymphadenectomies</td>
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<td>Radiation therapy</td>
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<tr>
<td>Chemotherapy</td>
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<td>SLNB: sentinel lymph node biopsy</td>
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no adverse histology and negative adenopathies or sentinel lymph node. In advanced loco-regional disease or remote metastasis, whenever the general conditions of the patient so allow, chemotherapy is recommended; this achieves an initial improvement, but there is no evidence that it increases survival. Agents with platinum combined with etoposide are used; clinical trials are under way with imatinib mesylate, c-kit protein (CD117), survivin, VEGFR-2/PDGF-alpha and anti-CD56. Acting as molecular targets, these may contribute to the success of the therapeutic agents currently in use.

Conclusions

PCNC is a tumour with a poor prognosis that appears at advanced ages. Its diagnosis is based on its clinical, cytological and immunohistochemical characteristics. It is primarily located in the head and neck. Intensive treatment must be applied to the primary tumour having regard for the tumour stage at the moment of diagnosis. The safety margins must be proportional to the tumour size and the treatment of loco-regional metastases is essential, without any consensus having been reached on the handling of N0 patients. It is currently advisable to use adjuvant radiation therapy after surgery even in stage I. It may, exceptionally, be possible to dispense with radiation therapy in highly favourable cases. Consideration must be given to the use of multiple chemotherapy in widespread tumours, in recurrent inoperable disease or in patients with remote metastases. The aggressiveness of the PCNC compels a meticulous lifelong monitoring of the patient. However, there is still hope of the possible introduction of anti-viral treatments in future.

Conflict of Interest

The authors declare no conflict of interest.

References