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Metastasis of malignant pleural mesothelioma to the scalp following chemotherapy: A case report and review of the literature --Borrador del manuscrito--

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Resumen:	Malignant pleural mesothelioma is a neoplasm involving mesothelial cells of the pleura. During the course of the disease both local and distant metastases may develop, although the latter are less common. As such it is rare for cutaneous metastases to appear as a solitary lesion on the scalp. Here we present the case of a 54-year-old woman with a 2-year history of unresectable left pleural mesothelioma treated with chemotherapy, who had developed a painful lump on the scalp one month prior to consultation. Skin metastases of mesothelioma must be differentiated from primary neoplasms, and immunohistochemistry is fundamental to determine the origin of such lesions, which can be correctly identified through the use of a panel of markers.
Revisores sugeridos:	FRANCISCO JAVIER VELASCO ALBENDEA, M.D FEA ANATOMIA PATOLOGICA, Complejo Hospitalario Torrecardenas fjalbendea@gmail.com ANATOMOPATOLOGO CON AMPLIA EXPERIENCIA EN LA ESPECIALIDAD, ACTUALMENTE FIGURA COMO REVISOR DE LA REVISTA ESPAÑOLA DE PATOLOGIA
Respuesta a los revisores:	Revisor nº1: -Se realiza revisión por un nativo de todo el texto corrigiendo los errores gramaticales -Se adicionan los porcentajes epidemiológicos de metástasis: referencia bibliográfica #17 Table2 Metastatic patterns of advanced MPM in the 21st century Local spreadDistant spread Nodal disease 65%Parenchymal lung metastases 27% Pleural effusion 64%Peritoneal/omental disease 24% Chest wall involvement 43%Bone metastases 20% Contralateral lung disease 36%Subcutaneous metastatic nodules 19% Pericardial infiltration 29%Visceral metastases 15% Pericardial effusion 12%Intramuscular metastases 4% Brain metastases 3% -Se incluye tabla de casos reportados de mesotelioma metastásico a cuero cabelludo Table 1. Literature review of scalp metastases from MPM CaseYear of publicationAge (Years)Sex M/FType of mesotheliomaSubtype of cutaneous metastasesTreatmentOutcome/ Follow up 11968865MPleuralSarcomatoidNRNR 22007567MPleuralEpithelioidChemotherapyAlive at 2 years and 7 months after the biopsy 32007647MPleuralBiphasicChemotherapyDeceased within 6 months 42009954MPleuralEpithelioidChemotherapyNR

	<p>52020 (current case)54FPleuralEpithelioidChemotherapyDeceased within 1.5 month following cutaneous biopsy</p> <p>Abbreviations: F, female; M, male; NR, not reported</p> <p>-No disponemos de foto clínica, debido a que el médico tratante pensó que la lesión se correspondía con un quiste infundibular inflamado</p> <p>-Se incluye imagen de TAC (Figure 1)</p> <p>-No se realizaron estudios de NGS, como tampoco genéticos. Debido a que la paciente fallece un mes y medio después del diagnóstico de la metástasis</p> <p>Revisor nº2:</p> <p>-El texto ha sido revisado por completo, subsanando los errores gramaticales (revisión por un nativo)</p> <p>-En el apartado final del case report se menciona que la paciente fallece un mes y medio después del diagnóstico de la metástasis (The patient died a month and a half after this diagnosis).</p> <p>-Se revisa la referencia bibliográfica #17 adaptándola a las normas de la revista, pasa a ser la #18 debido a que se incluye una referencia más al manuscrito:</p> <p>Husain AN, Colby TV, Ordóñez NG, Craig Allen T, Attanoos RL, Beasley MB et al. Guidelines for Pathologic Diagnosis of Malignant Mesothelioma 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2018;142:89-108.</p>
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To,
The Editor

Please find enclosed the manuscript entitled “Metastasis of malignant pleural mesothelioma to the scalp following chemotherapy: A case report and review of the literature”, which we are submitting for possible publication in the brief report section of your journal.

The authors are Sandra Liliana Quijano Moreno and Mario Garcia de Lacoba. This is an original manuscript, and is not currently being reviewed by any other journal. The paper provides a brief description of a metastases of malignant pleural mesothelioma to the scalp in a 54-year-old woman with a 2-year history of unresectable left-sided malignant pleural mesothelioma of the epithelioid type was treated with chemotherapy. To date, only four cases of malignant pleural mesothelioma with scalp metastases exist in the scientific literature all in males. Making this description of the fifth such case, the first reported in a woman. This manuscript complies with the ethical responsibilities laid down in the journal's requirements: research procedures were in accordance with the ethical rules of the committee on human experimentation, and with the World Medical Association Declaration of Helsinki. The participants' right to privacy and confidentiality was fully guaranteed; no identifying data was included in the text or images. Informed consent was obtained from all patients both for participation in the study and for the publication of the results. The authors of the manuscript have no conflict of interest to declare. All the authors read and approved this manuscript. The journal's requirements regarding authorship have been fully observed.

Sandra Liliana Quijano Moreno:

- Conception or design of the work, or the acquisition, analysis, or interpretation of data for the work
- Drafting the work or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work

Mario Garcia de Lacoba:

- Analysis, or interpretation of data for the work
- Drafting the work or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work

Yours faithfully,

Sandra Liliana Quijano

Sandra Liliana Quijano Moreno

A handwritten signature in black ink, appearing to be 'M. Garcia de Lacoba', with a stylized, overlapping structure.

Mario Garcia de Lacoba

Ética de la publicación

1. ¿Su trabajo ha comportado experimentación en animales?:

No

2. ¿En su trabajo intervienen pacientes o sujetos humanos?:

No

3. ¿Su trabajo incluye un ensayo clínico?:

No

4. ¿Todos los datos mostrados en las figuras y tablas incluidas en el manuscrito se recogen en el apartado de resultados y las conclusiones?:

Sí

Metastasis of malignant pleural mesothelioma to the scalp following chemotherapy: A case report and review of the literature

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Introduction

Cutaneous metastases of malignant pleural mesothelioma (MPM) are rare events that can occur through the direct extension of the neoplasm as a local or distant metastasis. In general, skin metastases develop after the initial diagnosis and later on in the evolution of the disease. Skin involvement can occur through 3 main routes: regional spread via lymphatics, direct extension within surgical scars and distant metastasis via hematogenous spread ¹⁻⁶. As the clinical findings are usually subtle the diagnosis of these metastases requires a high degree of suspicion. Their identification reflects the existence of a disseminated malignant neoplasm, and it may even allow an as yet undiagnosed neoplasm to be detected or signify an early sign of tumour recurrence after a period of remission. In most cases, these metastases have a poor prognosis. Distant metastases occur late in the disease course and they are mostly thought to represent local invasion, usually detected at autopsy ⁷. By contrast, the most frequent causes of benign painful lumps on the scalp of adults are epithelial inclusion cysts or tricholemal cysts. To date, only four cases of malignant pleural mesothelioma with scalp metastases exist in the scientific literature, all in males (Table 1)^{5,6,8,9,11}. Making this description of the fifth such case, the first reported in a woman.

Table 1. Literature review of scalp metastases from MPM

Case	Year of publication	Age (Years)	Sex M/F	Type of mesothelioma	Subtype of cutaneous metastases	Treatment	Outcome/ Follow up
1	1968 ⁸	65	M	Pleural	Sarcomatoid	NR	NR
2	2007 ⁵	67	M	Pleural	Epithelioid	Chemotherapy	Alive at 2 years and 7 months after the biopsy
3	2007 ⁶	47	M	Pleural	Biphasic	Chemotherapy	Deceased within 6 months
4	2009 ⁹	54	M	Pleural	Epithelioid	Chemotherapy	NR
5	2020 (current case)	54	F	Pleural	Epithelioid	Chemotherapy	Deceased within 1.5 month following cutaneous biopsy

Abbreviations: F, female; M, male; NR, not reported

Case report

A 54-year-old woman with a 2-year history of unresectable left-sided MPM (Fig. 1a) of the epithelioid type was treated with chemotherapy (6 cycles of cisplatin and pemetrexed), developing Grade 2 neurotoxicity in the hands and feet. Six months after starting the treatment the lesion had grown and it had invaded the thoracic wall (Fig. 1b). Two years later, the disease had progressed, with deposition of peritoneal implants and the appearance of a painful lump on the scalp that had been detected one month prior to the consultation. Clinical examination identified a subcutaneous lesion of approximately 4 mm on the scalp (vertex) that was not ulcerated, that was mobile and that was painful when touched. The patient did not have any other relevant history of pathological events and exposure to asbestos were ruled out. The scalp lesion was resected and sent to the Pathological Anatomy Laboratory with a diagnosis of an inflamed infundibular cyst. The sample was a cutaneous wedge excision measuring 0.7 x 0.5 x 0.4 cm and with no apparent lesions in the epidermis. However, a subcutaneous 3 x 3 mm lump of a whitish coloration was detected in a section.

No histopathological alterations were observed in the epidermis. However, a well-circumscribed, well-delimited and non-encapsulated nodular lesion was identified at the border zone between the papillary and reticular dermis (Fig. 2a), with a neo-formative appearance. This lesion formed tubules and strands through the proliferation of loosely cohesive atypical epithelioid cells with eosinophilic cytoplasm, prominent nucleoli and mild nuclear pleomorphism, with the presence of mitotic figures and apoptotic bodies (Fig. 2b). The lesion was accompanied by scarce lymphocytic infiltration. The neoplastic cells were strongly immunoreactive for Calretinin (Fig. 3a), weakly positive for CK5/6 (Fig. 3b), WT1 (Fig. 3c), and D-240 (Fig. 3d), yet they were negative for S-100, Melan-A, HMB-45, CK7, CD31, CD34. The morphological and immunohistochemical findings led to a diagnosis of MPM metastasis of an epithelioid type. The patient died a month and a half after this diagnosis.

Discussion

Malignant mesothelioma (MM) is a mesodermal neoplasm originating from multipotent cells that line the mesothelium, the subserosa of pleura/pericardium/peritoneum^{1-4,8-12} and the tunica vaginalis of the testes^{11,12}. Approximately 70-90% of pleural mesotheliomas are associated with exposure to asbestos^{3,4} and they are generally

categorised into three different pathological forms: epithelioid (EMM 60%), sarcomatoid (10-20%) and biphasic (20-30%)^{3,4,10}. The most frequent sites of metastasis associated with these tumours are regional lymph nodes, lung, liver, adrenal glands, kidneys^{1-7,9,10}, as well as a few cases of subcutaneous nodules^{10,13}. In post-mortem studies, extrapleural dissemination of these tumours has been detected in the liver (31.9%), spleen (10.8%), thyroid gland (6.9%) and brain (3%)^{7,10,11,14}, while cutaneous metastases from MPM are rare^{1,4,5,11}. Exceptionally, distant metastases have also been diagnosed¹⁰ in the lips^{1,5,10}, oral cavity (floor of the mouth-gingival)⁴, face^{1,3,5}, umbilicus^{5,7,12}, scalp^{5,6,8-9}, cerebellum⁶, fingers¹, neck¹⁵, tongue^{5,7,13}, trunk⁵, flank^{2,5}, abdominal wall⁵, bone⁴, upper back¹¹, skeletal muscle⁵, and lacrimal gland¹⁶.

With a changing current landscape of cancer diagnosis and treatment, increased areas of unusual metastases have been published as case reports. With no standard second-line therapies for MPM. Table 2 summarizes the most comprehensive and up-to-date pathologic database collected along 24 years from 1992 to 2016 for a cohort of 165 MPM-diagnosed and chemotherapy-treated patients¹⁷.

Table 2. Metastatic patterns of advanced MPM in the 21st century

Local spread	Distant spread
Nodal disease 65%	Parenchymal lung metastases 27%
Pleural effusion 64%	Peritoneal/omental disease 24%
Chest wall involvement 43%	Bone metastases 20%
Contralateral lung disease 36%	Subcutaneous metastatic nodules 19%
Pericardial infiltration 29%	Visceral metastases 15%
Pericardial effusion 12%	Intramuscular metastases 4%
	Brain metastases 3%

Immunohistochemistry is essential to define the origin of a metastasis adequately¹ and there is a panel of antibodies against several markers that is very useful to diagnose metastases from MPM¹⁵. Thus, in the case of EMM the following markers are used¹⁸⁻¹⁹:

- Calretinin is demonstrated in nearly all epithelioid mesotheliomas¹⁸ (>80%)¹⁹ the staining is often strong and diffuse and is both nuclear and cytoplasmic^{18,19}.
- Cytokeratin (CK) 5/6 expressed in 75-100% of mesotheliomas¹⁸, the staining is cytoplasmic.

1 - The WT-1 transcription factor approximately 70-95% of mesotheliomas show nuclear
2 positivity¹⁸.

3
4 - Podoplanin D-240 about 90–100 % of mesotheliomas show positivity along the cell
5 membranes¹⁸.

6
7
8 Unlike other markers, calretinin is currently considered the most sensitive marker to
9 diagnose EMM^{5,11,15,18,19}. As it is expressed in all types of mesotheliomas¹⁸, the failure
10 to detect this marker would rule out the diagnosis of this clinical entity. Focal calretinin
11 staining may be detected in adenocarcinomas but diffuse staining is rarely observed in
12 such tumours. There is no standard proportion of tumour cells immunoreactive to this
13 marker that could be considered as a valid parameter, yet a consensus threshold of 10%
14 is generally regarded as a positive response¹⁸. Cutaneous metastases of MPM must be
15 distinguished from adenocarcinomas, squamous cell carcinomas, epithelioid
16 hemangioendotheliomas, angiosarcomas, lymphomas and malignant melanoma¹. The
17 average 6-month survival rate after a diagnosis of mesothelioma is 50%, the interval
18 between the diagnosis of the primary tumour and the onset of metastasis ranging from 2
19 to 3 years, depending on the primary tumour. The prognosis of MPM is poor, with an
20 average survival of 12 months^{3,5} and with local disease progression the usual cause of
21 death³.

22 Conclusions

23 Distant subcutaneous metastases of MPM are rare and only a few cases have been
24 reported. These metastases are physically indistinguishable from other types of lesions
25 and therefore, they remain underdiagnosed and must be clearly distinguished from
26 primary or other types of metastatic neoplasms. As such, apart from a good knowledge
27 of the patient's clinical history, other possible origins must be ruled out by using
28 complete panel immunohistochemical markers in order to determine the true nature of
29 the lesion adequately. The presence of cutaneous metastasis usually implies the
30 presence of a systemic and generalized disease with a high rate of mortality. The mean
31 survival time from the diagnosis of metastases is around one year and the cause of death
32 is attributed to disease progression, although the prognosis may vary considerably
33 depending on the nature of the primary tumour.

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Figure legends

Figure 1

a. CT scan shows a pleural thickening in the left hemitorax, with involved mediastinal pleura and calcified pleural plaque in the right base.

b. Progression of the left MPM, with invasion of the thoracic wall (arrow)

Figure 2

a. Low-power panorama view of a well-circumscribed non-encapsulated neo-formative lesion, located in the dermis and surrounded by adnexal structures (H&E).

b. The lesion is constituted by a proliferation of epithelioid cells that form tubules, and that have an eosinophilic cytoplasm and prominent nucleoli (H&E 400 x).

Figure 3

a. Low-power panorama view shows strong and diffuse nuclear/cytoplasmic immunoreactivity for calretinin.

b. Low-power panorama view shows cytoplasmic immunostaining for CK5/6.

c. WT1 nuclear immunostaining (WT1, 100 x).

d. Strong D-240 immunoreactivity along the apical cell membrane (D-240,100 x).