Quiz

Correct answer to the quiz. Check your diagnosis

Case report

Pleural mesothelioma metastasis of the scalp

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Mesothelioma is a locally aggressive malignant tumor that arises on the mesothelial surfaces of the pleura, peritoneum and tunica vaginalis. There are three histologic subtypes of mesothelioma: epithelioid, biphasic, and sarcomatoid. Pleural mesothelioma is usually characterized by diffuse pleural thickening. Disease progression is characterized by local invasion of the chest wall and lung. Lymphatic metastasis is rare and hematogenous metastasis is much rarer. The purpose of these case reports is to emphasize that pleural mesothelioma metastases can occur in unexpected places and to contribute to the literature.

Key words: immunohistochemistry, mesothelioma, pleural, p16/CDKN2A, scalp.

Introduction

Mesothelioma is a locally aggressive malignant tumor that arises on the mesothelial surfaces of the pleura, peritoneum and tunica vaginalis. Mesothelioma occurs predominantly in men, and risk increases with age [1, 2]. The association with asbestos exposure is especially strong for the pleural site, where 80% of patients report a history of asbestos exposure, often with development of the disease between 20–60 years later [1, 3]. Less frequently, prior radiation exposure has been suggested as a causative agent in pleural mesothelioma [2]. Familial forms of pleural mesothelioma with autosomal dominant inheritance have been reported in the Cappadocia region of Turkey (Tuzkoy, Karain, and Sarihidir) [2].

Asbestos exposure is environmental and occupational. In some rural towns and villages in Turkey, tremolite type asbestos, called white soil, is widely found in nature and is widely used for thermal insulation on the roofs and walls of buildings. Asbestos exposure in Turkey is endemic in Sivas, Eskişehir, Kütahya, Bilecik, Yozgat and Diyarbakır. Exposure to erionite has been reported in rural areas in the Nevşehir-Ürgüp region. Since it is endemic in these regions, Turkey is among the most common countries in the world in terms of mesothelioma, with a rate of 2.9/100,000 in Eskişehir [4]. There are three histologic subtypes of mesothelioma: epithelioid (most common), biphasic, and sarcomatoid [5]. According to the SEER database, the median survival in patients diagnosed with epithelioid, biphasic, and sarcomatoid mesotheliomas of the pleura who underwent surgical treatment was 19, 12, and 4 months, respectively [6].

Pleural mesothelioma often characterized by diffuse pleural thickening and nodular areas can be observed in areas of diffuse thickening.

Spread generally occurs along interlobar fissures, extending into the lung, diaphragm, and/or chest wall. Mediastinal involvement, with direct invasion of pericardium and other mediastinal structures, is common.

Lymphatic spread is observed in mesothelioma. Mediastinal lymphadenopathy may occur without

the presence of hilar lymphadenopathy. Pericardial, peridiaphragmatic, internal mammary, supraclavicular, abdominal, and intercostal lymph node involvement is frequent during progression [7–9].

Although development of early symptomatic systemic metastases is unusual, tumor involvement of extrathoracic sites is common in end-stage disease. Mesothelioma dissemination most commonly occurs via invasion of contiguous structures, with transdiaphragmatic spread, invasion of the liver or spleen, pericardial invasion, and involvement of the contralateral pleural space.

In mesothelioma, rare hematogenous metastases to the lung, liver, adrenal glands, bone, kidney or brain can be observed. However, metastases to the skin and scalp are very rare [8].

The purpose of these case reports is to emphasize that pleural mesothelioma metastases can occur in unexpected places and to contribute to the literature.

Case reports

The first case, a 53-year-old male patient, was admitted to the outpatient clinic with the complaint of a painless nodular lesion on the scalp. The histopathological features of the biopsy were primarily reported in favor of "malignant skin adnexal tumor". He was referred to our laboratory for immunohistochemical (IHC) staining for the differential diagnosis of skin adnexal tumors and melanoma.

Since the paraffin blocks were brought by the patient's relatives, a detailed history could not be obtained. The patient's health data could not be accessed from the national electronic health system.

In histological examination the tumor cells typically display eosinophilic cytoplasm, round nuclei with coarse chromatin, prominent nucleoli and frequent mitoses (Fig. 1A). Epidermis and skin appendages were not seen in the sections. No intracytoplasmic pigment was observed. Histopathological differential diagnosis included squamous cell carcinoma, basal cell carcinoma, malignant skin appendage tumors, metastatic carcinomas, malignant melanoma, lymphomas, and vascular tumors.

Immunochemical stains of the tumor sections were positive for pan-cytokeratin and epithelial membrane antigen (EMA) and negative for S100, Sox10, CD30, ERG, CD34, BerEP4, P63 and PAX8. Thus, squamous and basal cell carcinoma of the skin, malignant skin adnexal tumors, metastatic carcinomas, melanoma, anaplastic large cell lymphoma of CD30 positive skin and vascular tumors were excluded.

The patient was re-evaluated. It was learned that a pleural biopsy was performed 5 months ago. The report showed the diagnosis as "mesothelioma, epithelioid type (solid variant)". In the additional IHC staining panel, calretinin, podoplanin, WT1, and cytokeratin 5/6 (CK 5/6) stained positive (Fig. 1B, C) MTAP and BAP1 were studied. Approximately 90%

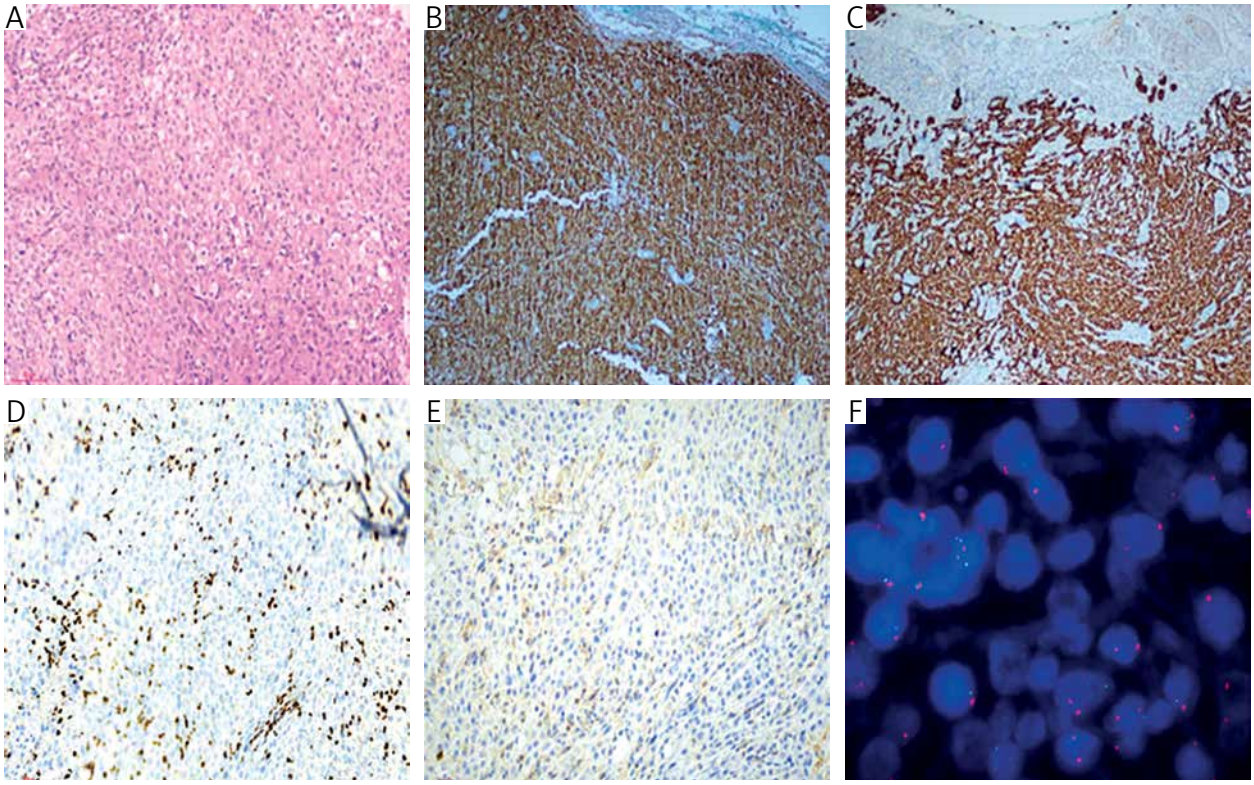

Fig. 1. Case 1 – scalp biopsy. **A)** Neoplastic proliferation composed of epithelioid cells (HE, 400x); **B**, **C)** calretinin and CK 5/6 (100x); **D**) loss of BAP1 expression (100x); **E**) loss of cytoplasmic MTAP (100x); **F)** CDKN2A/p16 deletion by fluorescent in situ hybridization

of tumor cells showed cytoplasmic MTAP and 100% BAP1 loss (Fig. 1D, E) 40% homozygous deletion was observed in the CDKN2A/p16 test performed by fluorescent *in situ* hybridization (FISH) technique (Fig. 1F, Table I).

The second case was a 63-year-old male patient who presented to the dermatology outpatient clinic with a painless, fixed nodular lesion on the scalp. Punch biopsy was taken from the mass and sent to the pathology laboratory. It was learned that the patient, whose history was taken from the hospital automation system, lived in Diyarbakır/Ergani, where asbestos is endemic, and was diagnosed with epithelioid type mesothelioma 2 years ago as a result of pleural biopsy.

When the mass on the scalp was examined, a tumor with eosinophilic cytoplasm, large hyperchromatic nuclei and prominent nucleoli filling the dermis was observed. (Fig. 2A, B) Skin punch biopsy was examined together with previous pleural biopsies taken from the archive of the patient. It was included in the differential diagnosis because of its known history with mesothelioma metastasis, squamous cell carcinoma, melanoma, CD30 positive anaplastic large cell lymphoma of the skin, metastatic carcinomas, angiosarcoma and malignant skin adnexal tumors. The IHC panel was also expanded for these differential diagnoses. Pancytokeratin and calretinin stained positive. Carcinoma metastases and skin adnexal tumors were excluded with berEP4 negativity, angiosarcoma with ERG negativity, and melanoma with S100 and Sox10 negativity. Loss of cytoplasmic MTAP was observed in approximately 80% of tumor cells. No loss of BAP1 was observed in the examination of previous slides in the pleural biopsy of the case (Fig. 2C, D) 30% p16 homozygous deletion was observed in the FISH test (Fig. 2E, F, Table I).

The cases were reported as epithelioid mesothelioma metastases based on histomorphological, immunohistochemical and molecular findings.

The first patient died 8 months after the initial diagnosis and 3 months after the scalp metastasis was detected and the second patient died 2 years after the initial diagnosis and 1 month after the scalp metastasis.

Discussion

Pleural mesothelioma is characterized by diffuse pleural thickening. Local invasion of the chest wall and lung may be seen. Lymphatic spread to mediastinal lymph nodes is most common. Pericardial, peridiaphragmatic, internal mammary, supraclavicular, abdominal and intercostal lymph nodes are also involved. Hematogenous spread is very rare; metastasis to the lung, liver, adrenal glands, bone, kidney or brain has been reported [5]. Skin and scalp metastases are much rarer.

Mesothelioma scalp metastasis was first reported by Bazex *et al.* [10]. Nineteen skin and 5 scalp metastases have been reported in the English literature. Primary mesothelioma to the pleura constitutes 85% of the reported cases of cutaneous metastasis and peritoneal mesothelioma 15% of the reported cases. All cases with cutaneous metastases originating from the peritoneum were epithelioid, approximately 60% of cases of pleural mesothelioma were of the epithelioid subtype, 23% were of the sarcomatoid subtype, and 17% were of the biphasic subtype. Three of the reported scalp metastases were epithelioid, one was sarcomatoid and one was biphasic [7]. Both of the presented cases originated from the pleura and were epithelioid type (Table II).

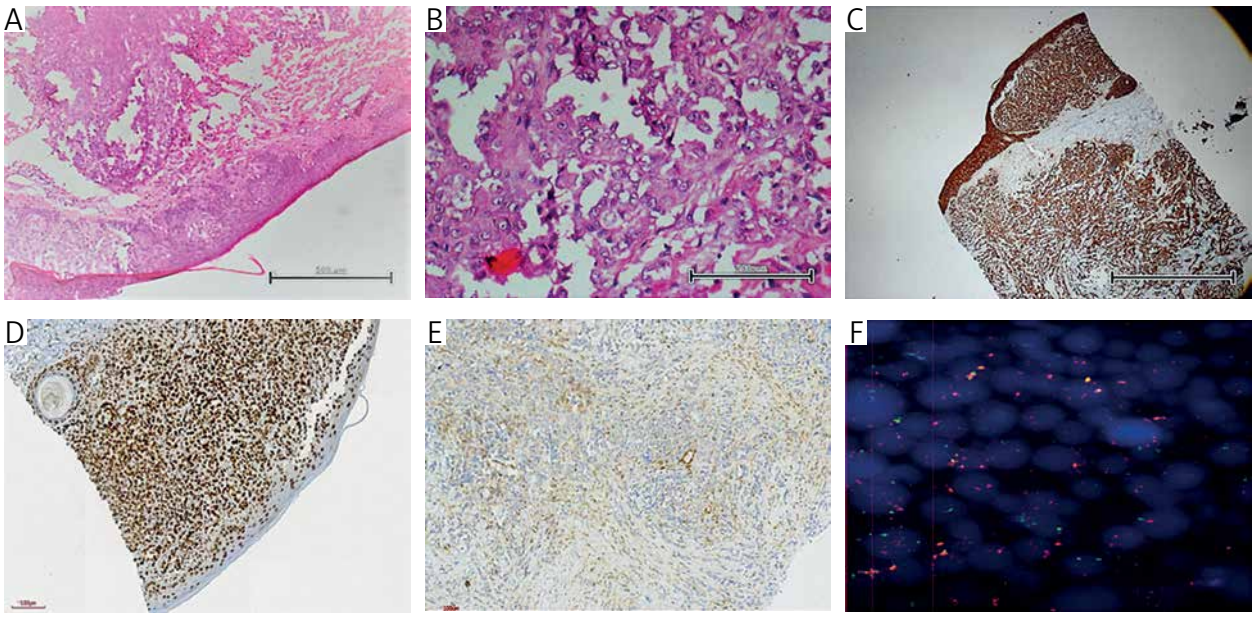

Fig. 2. Case 2. **A, B)** Scalp biopsy neoplastic proliferation in dermis (HE, 100×, 400×). **C, D)** PanCK and BAP1 (100×). **E)** Loss of cytoplasmic MTAP (100×). **F)** CDKN2A/p16 deletion by fluorescent in situ hybridization

Table I. Immunohistochemical and molecular features of our presented cases

Case	BAP1 expression in scalp metastases	Loss of MTAP cytoplasmic staining in scalp metastases (%)	Scalp metastasis P16 FISH study result	Pleural biopsy BAP1 expression
1	Total loss of expression	80	Homozygous deletion	Total loss of expression
2	No loss of expression	80	Homozygous deletion	No loss of expression was observed

FISH – fluorescent in situ hybridization

Table II. Summary of cases in the literature

Cases	Year of publication	Age (years)	Sex M/F	Type of mesothelioma	Subtype of cutaneous metastases	Outcome/ Follow-up	FISH analysis	MTAP IHC	BAP1 IHC
1	1968	65	M	Pleural	Sarcomatoid	NR	NR	NR	NR
2	2007	67	M	Pleural	Epithelioid	Alive at 2 years and 7 months after the biopsy	NR	NR	NR
3	2007	47	M	Pleural	Biphasic	Deceased within 6 months	NR	NR	NR
4	2009	54	M	Pleural	Epithelioid	NR	NR	NR	NR
5	2020	54	F	Pleural	Epithelioid	Deceased within 1.5 month following cutaneous biopsy	NR	NR	NR
6 (current case)	2023	53	M	Pleural	Epithelioid	Deceased within 8 months following cutaneous biopsy	Homozygous deletion	Loss of expression	Loss of expression
7 (current case)	2023	63	M	Pleural	Epithelioid	Deceased within 1 month following cutaneous biopsy	Homozygous deletion	Loss of expression	Diffuse positive

F – female, FISH – fluorescent in situ hybridization, IHC – immunohistochemical, M – male, NR – not reported

The majority of reports demonstrated positive staining with calretinin, cytokeratins (especially CK 5/6 and CK 7), vimentin, EMA, thrombomodulin, HMBE-1, and Wilms' tumor (WT)-1. Commonly used negative stains included carcinoembryonic antigen, S100, TTF-1, Leu M1, Factor VIIIRA, cluster of differentiation (CD)-31, CD34, B72.3, and human melanoma black (HMB)-45 [10]. Loss of BAP1 expression and loss of MTAP cytoplasmic staining are reported as diagnostic [11]. In our cases, calretinin, CK 5/6, pan-cytokeratin, and WT-1 stained positive and loss of MTAP cytoplasmic staining was observed. Pleural biopsy and scalp metastasis of the first case showed 100% loss of BAP1 expression. BAP1 expression was preserved in the pleural and scalp metastases of the second case. It has been reported in the literature in 42% of cases that BAP1 expression is preserved in mesothelioma [11]. The number of cases in which BAP1 expression was preserved is low, and the loss in our second case contributed to the literature.

In the FISH test in the scalp metastases, homozygous p16 deletion was observed in 40% of tumor cells in the first case and 30% in the second case. Loss of MTAP cytoplasmic staining was observed in our cases.

As reported in the literature, MTAP cytoplasmic loss was correlated with FISH homozygous deletion [13].

Kanbay *et al*. reported scalp metastasis of mesothelioma and the patient died at the 6th month after treatment. Yetiskin *et al*. detected a nodule on the scalp of the occipital region and concurrent supraclavicular lymphadenopathy in a patient with pleural mesothelioma 1 year after treatment [14]. The scalp mass was confirmed by immunohistochemical study and diagnosed as mesothelioma metastasis. The patient was reported to have died 4 years after the initial diagnosis. In this study, scalp metastasis was interpreted as a poor prognostic finding [8].

The fact that the initial diagnosis of our cases was pleural, epithelioid type and that they were elderly males is consistent with the findings in the literature. In addition, the fact that both of our patients experienced metastasis to the scalp shortly after the initial diagnosis and died within 6 months after the diagnosis of metastasis supports the poor prognosis reported in the literature.

A retrospective archive search revealed that 570 mesothelioma cases were reported in the last 10 years in our clinic, which is located in an asbestos endemic region. Lymph node metastases were observed in 8 of these cases. Metastases most commonly occurred to mediastinal lymph nodes, followed by internal mammary, cervical and supraclavicular lymph nodes. Apart from the two cases presented in our archive, hematogenous metastasis in the femur was observed in one case.

Conclusions

We reported two extremely rare cases with scalp metastasis of pleural mesothelioma. The diagnosis was based on histologic and IHC findings and cytogenetic testing. BAP-1, MTAP IHC and cytogenetic tests in scalp and skin metastases have not been reported in the literature. In the present cases, these tests were performed, BAP1 expression was preserved in one case and they were atypically localized, which contributed to the literature and emphasized the importance of BAP1 and MTAP in the diagnosis. It has been reported in the literature that loss of BAP1 may not be present in all mesotheliomas, and it has been emphasized that it is not diagnostic on its own.

Scalp metastases are associated with poor prognosis due to uncontrolled disease and hematogenous spread. When evaluating skin biopsies, the patient's history should be known as in all localizations and mesothelioma metastasis to unexpected localizations should not be forgotten. Differential diagnosis from primary adnexal neoplasms, melanoma and metastatic tumors is required when it occurs in endemic areas, especially in atypical localizations such as the scalp.

The authors declare no conflict of interest.

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