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Title

Sarcomatoid mesothelioma originating from mesothelioma in situ: Are methylthioadenosine phosphorylase loss and *CDKN2A* homozygous deletion poor prognostic factors for preinvasive mesothelioma?

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Abstract

The diagnosis of mesothelioma in situ (MIS) is challenging with conventional diagnostic approaches. Although recent advances in genomic-based assays have made it possible to diagnose MIS, the prognosis, treatment indications, and prognostic factors remain unclear. Previous reports have shown that MIS progresses to invasive mesothelioma; however, to the best of our knowledge, progression to sarcomatoid mesothelioma has not yet been reported. A 73-year-old man was diagnosed with MIS associated with methylthioadenosine phosphorylase (MTAP) loss and a *CDKN2A* homozygous deletion. Strikingly, pathological examination revealed that the MIS lesion had progressed to sarcomatoid mesothelioma. In analyses of previously reported cases and our case, MIS with a *CDKN2A* homozygous deletion or MTAP loss progressed to invasive mesothelioma earlier than that without them, indicating that a *CDKN2A* homozygous deletion and MTAP loss could be poor prognostic factors. Genomic analyses might be useful for predicting the prognosis of MIS and contributing to an optimal treatment.

Key words

CDKN2A, malignant mesothelioma in situ (MIS), methylthioadenosine phosphorylase (MTAP), sarcomatoid malignant mesothelioma

Introduction

Malignant mesothelioma is a highly lethal tumor. One of the reasons for this is delay in detection, as it is often diagnosed at an advanced stage [1]. However, early detection and ablation or excision may increase the chances of curing this tumor like other malignant tumors involving other organs.

Whittaker et al. were the first to advocate the possibility of histological diagnosis of mesothelioma in situ (MIS) [2], but the diagnosis of MIS remains challenging due to two main problems. First, it is difficult to morphologically separate malignant mesothelioma from reactive mesothelial proliferations [3]. Second, it is challenging to determine whether the lesion is a true MIS or a surface spread of invasive mesothelioma. Recent advances in genomic-based assays, represented by the detection of loss of breast cancer 1 (BRCA-1) associated protein 1 (BAP1) and/or methylthioadenosine phosphorylase (MTAP) by immunohistochemistry (IHC) and/or a *CDKN2A* homozygous deletion by fluorescence in situ hybridization (FISH), have greatly improved the first problem [4]. It is difficult to completely solve the second problem, but multidisciplinary discussions including imaging studies and intraoperative findings can help distinguish true MIS from the pleural surface spread of invasive mesothelioma.

Although the approach to definitive diagnosis remains controversial, MIS is newly included in the fifth edition of the World Health Organization classification defined as “preinvasive single-layer surface proliferation of neoplastic mesothelial cells [5]”. However, the prognosis, indications for treatment, and prognostic factors remain unclear.

Among the reported cases of MIS that have been diagnosed based on IHC and/or FISH, several cases progressed to invasive disease [6-9] (Table 1). However, to the best of our knowledge, no previous report has described the progression to sarcomatoid mesothelioma. We previously reported a case of MIS that was diagnosed by MTAP loss and homozygous deletion of *CDKN2A* [10]; however, the lesion progressed to invasive sarcomatoid mesothelioma. We describe our experience with an extremely rare case of sarcomatoid mesothelioma that developed from MIS during a 25-month follow-up.

Case report

The case presentation before the diagnosis of MIS is shown in a previous report [10]. A 73-year-old man with occupational asbestos exposure visited our hospital with cough and chest pain. Imaging studies showed a large amount of right pleural effusion with mild pleural thickening. Intraoperatively, although video-assisted thoracic surgery (VATS) was performed in the right thoracic cavity, multiple plaques were detected; however, the pleura was smooth with no visual nodules. All five right pleural biopsy specimens revealed a single layer of atypical mesothelial cells that had lost MTAP (clone 2G4, 1:200, and Abnova) but not BAP1 (clone C-4, 1:100, Santa Cruz) (Figure 1a–e). Using SureFISH (Agilent Technologies; *CDKN2A* probe, red label; chromosome 9 centromeric probe, green label), proliferative mesothelial cells showed a *CDKN2A* homozygous deletion (Figure 1f), leading to the diagnosis of MIS. After 7 months, a biopsy was performed on the left side. There was no atypia, MTAP loss, or *CDKN2A* deletion in monolayer-proliferating mesothelial cells; therefore, there was no evidence of mesothelioma.

We proposed extrapleural pneumonectomy, pleurectomy/decortication, or follow-up. The patient selected careful follow-up upon this diagnosis; hence, we performed computed tomography (CT) approximately every 6 months. Fourteen months after the first biopsy, a CT scan showed slight bilateral pleural effusion and partial thickening of the pleura on the both sides, probably due to postoperative changes and plaques. Irregular thickening of the right pleura was observed 19 months after the first biopsy, and the lesion became clearly recognizable nodular thickening 25 months after the first biopsy. We assessed this lesion radiologically as progressive mesothelioma at this time, and performed a CT-guided needle biopsy 32 months after the first biopsy. Histologically, the tumor consisted of hyperchromatic atypical spindle cells in an abundant hyalinized collagenous stroma (Figure 1g–h). Myxomatous changes were also seen in the focal area. These cells were diffusely positive for cytokeratin IHEG1) (Figure 1i). In tumor cells, the expression of MTAP was lost and *CDKN2A* FISH showed significant (>50%) homozygous deletion, while BAP1 expression was retained (Figure 1j–l). Therefore, MIS progressed to invasive sarcomatoid mesothelioma with desmoplastic features within the biopsy sample.

The patient was receiving immunotherapy using a combination of nivolumab and ipilimumab, and a partial remission was seen on a CT scan. However, after the third course of treatment, a CT scan revealed the progression of the right pleural lesions and chest wall infiltration.

We performed palliative radiation therapy and planned to restart the chemotherapy after controlling the pain. We have confirmed 41 months of survival from the first biopsy and 8 months of survival from the third biopsy.

Review of the previous articles

We reviewed two case series and three case reports including our case to analyze the relationship between *CDKN2A* or MTAP status and prognosis [6-10]. Progression-free survival (PFS) was estimated using a Kaplan-Meier analysis, and differences were determined by a log-rank analysis. The statistical analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A P-value < 0.05 was considered statistically significant.

A total of 13 cases (including our case) have been reported as MIS. Ten cases of MIS progressed to invasive disease. The median time from the diagnosis of MIS to invasive mesothelioma was 60 months (range, 8–156 months). Among the 13 patients with MIS, a *CDKN2A* homozygous deletion was detected in three cases, and MTAP loss was detected in four cases (Table 1). The median PFS of the five cases with a *CDKN2A* homozygous deletion or MTAP loss was significantly shorter than that of the other eight cases (median PFS, 18 months versus 69 months, $p < 0.01$). Among the five cases of a *CDKN2A* homozygous deletion or MTAP loss, four cases progressed to invasive disease and only one case did not progress at the 12 months follow-up (Figure 2).

Discussion

Herein, we describe a case of sarcomatoid mesothelioma that developed from MIS with MTAP loss and a homozygous deletion of *CDKN2A*. The most impressive finding, in this case, is that MIS can progress to invasive sarcomatoid mesothelioma. The second issue is that *CDKN2A* deletion and MTAP loss in flat surface mesothelial cells can be high-risk factors for developing invasive mesothelioma.

First, MIS can directly progress to sarcomatoid mesothelioma. The concept of MIS has been postulated since the first case was reported in 1992 [2]. However, the subsequent analysis concluded that it is not possible to distinguish reactive mesothelial proliferation from MIS morphologically [3].

Diagnostic criteria, including in situ genomic analysis, have been established only in recent years [4, 6]. Thirteen MIS cases have been reported, including our case, since 2018 [6-10], and 10 cases have advanced to invasive disease so far. There was no detailed description regarding the subtype of invasive mesothelioma, but at least three of the 13 cases looked like the epithelioid type based on the figures, and there were no cases of conversion from MIS to the sarcomatoid type (Table1). To the best of our knowledge, this is the first reported case of sarcomatoid mesothelioma that progressed from MIS in the natural course. Although the whole tumor might still be classified as a biphasic if resected material was available, it was surprising to have only sarcomatoid component in biopsy sample.

Second, a *CDKN2A* deletion and MTAP loss could be high-risk factors for the progression of MIS to invasive mesothelioma. Since *CDKN2A* and *MTAP* are adjacent to 9p21, *CDKN2A* deletions often encompass MTAP loss [11]. *CDKN2A* deletion and MTAP loss are more prevalent in sarcomatoid mesothelioma (86–93%) than in epithelioid mesothelioma (65–71%). Conversely, BAP1 loss is more frequent in epithelioid mesothelioma (42–74%) than in sarcomatoid mesothelioma (0–37%) [12]. Several researchers have reported that mesothelioma with *CDKN2A* deletion has a worse prognosis than mesothelioma without it, which can be explained by the high frequency of the sarcomatoid type in *CDKN2A*-deleted tumors [13, 14]. Considering our results of the analysis on the relationship between *CDKN2A* or MTAP status and prognosis, a *CDKN2A* deletion and MTAP loss could be poor prognostic factors not only in invasive mesothelioma but also in MIS, and could contribute to the development of invasive mesothelioma from MIS. However, the number of cases of MIS was too small to make any conclusions on the relationship between genome-based abnormalities and the prognosis of MIS. Therefore, it is necessary to improve our understanding of MIS and accumulate more cases.

To date, the treatment approach and optimal surveillance of patients with MIS have not yet been decided. Although some authors have suggested that the progression of MIS is very slow [4], it is evident that there are aggressive cases, including early conversion to invasive tumor within 1 year and sarcomatous change, as in our case. The optimal follow-up period, including imaging studies, remains unclear, although may be altered depending on the risk of individual cases. Additionally, non-epithelioid subtypes have a significantly poorer prognosis and are less responsive to treatment overall than epithelioid subtypes [15]. The treatment option for sarcomatoid mesothelioma is also limited compared to that for epithelioid mesothelioma; for example, there is no indication for extrapleural pneumonectomy or

pleurectomy/decortication for sarcomatoid and biphasic mesothelioma. This indicates that re-biopsy is necessary when MIS progresses to invasive mesothelioma, although the timing of biopsy needs to be discussed.

In conclusion, we have presented a case of sarcomatoid mesothelioma that progressed from MIS with MTAP loss and a homozygous deletion of *CDKN2A*. There seems to be a variation in the clinical course of MIS than what was expected; therefore, re-biopsy in the case of progression after the diagnosis of MIS is necessary even if there is confidence in the invasiveness. If the characteristics of the developing cases from MIS are clarified, optimal treatment timing and long-term prognosis can be expected.

Declarations

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Conflicts of interest

The authors declare that they have no conflict of interest.

Availability of data and material

Not applicable

Code availability

Not applicable

Authors' contributions

Megumi Nishikubo, Naoe Jimbo, and Yugo Tanaka designed the case report and wrote the initial draft of the manuscript. Motoko Tachihara and Yoshimasa Maniwa contributed to sample and data collection, and Tomoo Itoh contributed to the pathological diagnosis. All authors reviewed the manuscript.

Ethics approval

Not applicable

Consent to participate

Not applicable

Consent for publication

Informed consent was obtained from all individual participants involved in this study.

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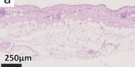
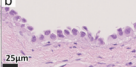
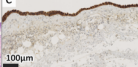
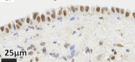
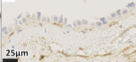
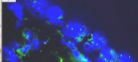
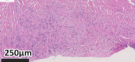
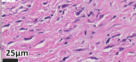
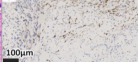
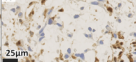
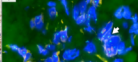
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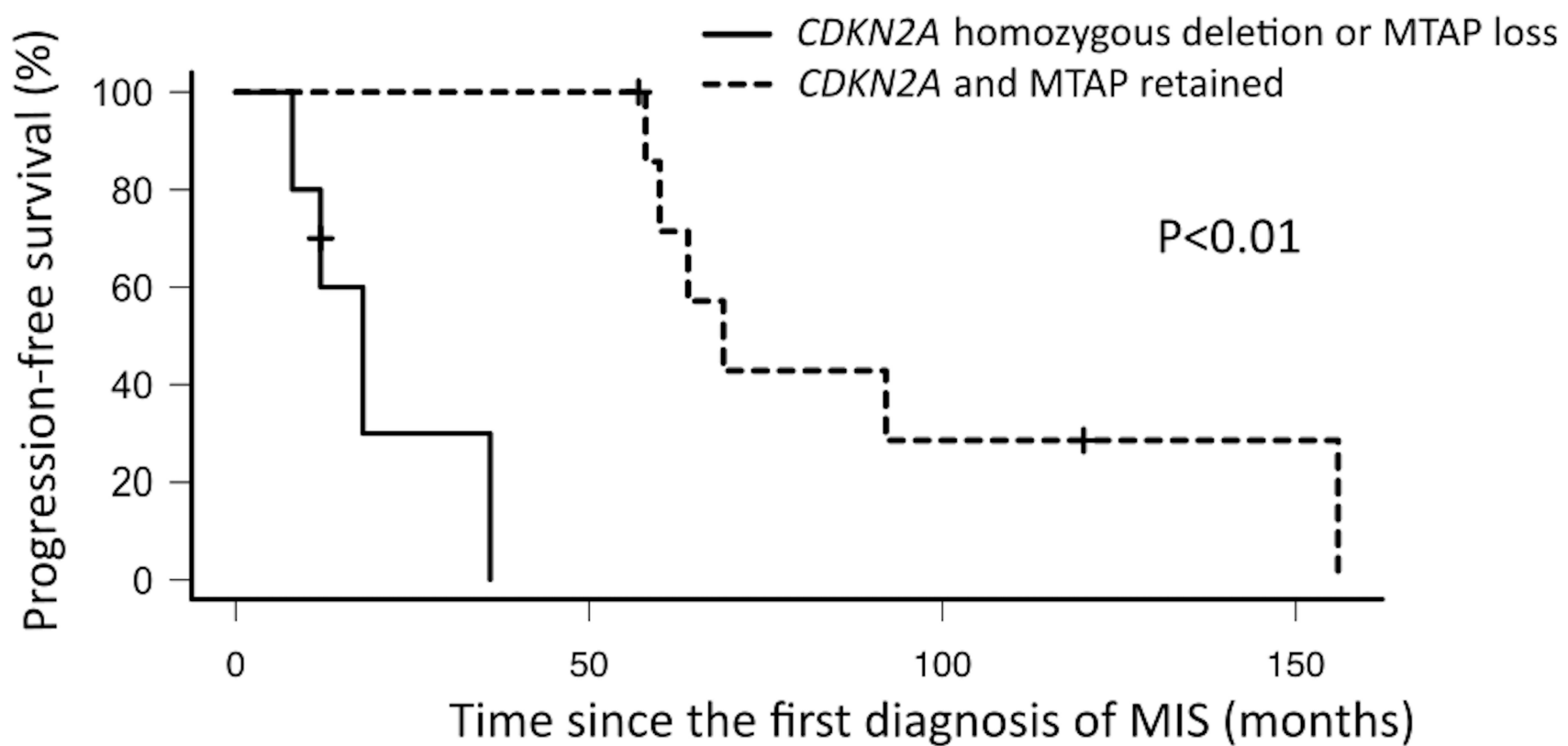
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Figure 1. Pathological analysis of pleural biopsy specimens at the first mesothelioma in situ (MIS) diagnosis by video-assisted thoracic surgery (VATS) biopsy (a–f) and after progression by computed tomography (CT)-guided needle biopsy (g–l).

The first right pleural biopsy shows a single layer of cuboidal mesothelial cells with no evidence of infiltration into the adipose layer (a, b) that is positive for calretinin (c). Breast cancer 1-associated protein 1 (BAP1) is retained in these mesothelial cells (d), whereas methylthioadenosine phosphorylase (MTAP) is lost (e). *CDKN2A* fluorescence in situ hybridization (FISH) showed a homozygous deletion (lack of red signal) in tumor cells (f). CT-guided biopsy of a progressive pleural tumor shows hyperchromatic atypical spindle cell proliferation in an abundant hyalinized collagenous stroma (g,h). The cells are partially positive for calretinin (i). BAP1 expression is retained in atypical cells (j), whereas MTAP is lost (k). *CDKN2A* FISH revealed a homozygous deletion in at least 50% of the spindle cells, whereas it demonstrated a normal pattern (two red signals and two green signals) in adjacent cells (arrow) (l).

Figure 2. Progression-free survival (PFS) of patients with a *CDKN2A* homozygous deletion or MTAP loss compared to those without, as estimated with a Kaplan-Meier analysis. The PFS is significantly shorter in cases of a *CDKN2A* homozygous deletion or MTAP loss.

a**b****c****d****e****f****g****h****i****j****k****l**



Number at risk

CDKN2A homozygous deletion
or MTAP loss

5

0

0

0

CDKN2A and MTAP retained

8

8

2

1

Table 1. A list of previously reported cases of mesothelioma in situ

Case	Age (years)/ Sex	Lesion	BAP1	MTAP	<i>CDKN2A*</i>	Progression to invasive mesothelioma	Subtype of invasive mesothelioma	Interval from first biopsy to invasive mesothelioma (months)	Follow-up term (months)	Author/Year
1	70/F	Pleura	Loss	Loss	Deleted	Yes	Epithelioid	36		Churg/2018 [7], 2020 [6]
2	71/F	Pleura	Loss	Not lost	Not done	Yes	N/A	64		Churg/2020 [6]
3	72/F	Pleura	Loss	Not lost	Not deleted	Yes	N/A	92		Churg/2020 [6]
4	68/M	Pleura	Loss	Not lost	Not deleted	Yes	N/A	58		Churg/2020 [6]
5	69/M	Pleura	Loss	Not done	Not deleted	Yes	N/A	69		Churg/2020 [6]
6	79/M	Pleura	Loss	Not done	Not done	Yes	N/A	60		Churg/2020 [6]
7	67/M	Pleura	Loss	Loss	Not deleted	No			12	Churg/2020 [6]
8	68/M	Pleura	Loss	Not lost	Not deleted	No			120	Churg/2020 [6]
9	76/M	Pleura	Loss	Not lost	Not deleted	No			57	Churg/2020 [6]
10	53/F	Peritoneum	Loss	Loss	Not deleted	Yes	N/A	12		Churg/2020 [6]
11	73/M	Pleura	Not lost	Loss	Deleted	Yes	Sarcomatoid	25		Our case [10]
12	50s/F	Pleura	Loss	Not lost	Not deleted	Yes	Epithelioid	156		Hidaka/2020 [9]

13	57/M	Pleura	Loss	Not done**	Deleted	Yes	Epithelioid	8		Haefliger/2021 [8]
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BAP1, BRCA-1 associated protein 1; F, female; M, male; MTAP, methylthioadenosine phosphorylase, N/A, not assessed.

* “deleted” indicates a homozygous deletion

**In case 13, MTAP loss was confirmed in the specimen only at the time when the diagnosis of invasive malignant mesothelioma was made.