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Immunohistochemical evidence of Aquaporin 1 (AQP1) in Fluoroedenite-induced mesotheliomas: a preliminary report

Giuseppe Angelico[1] , Antonio Ieni[1], Rosario Caltabiano[2], Saveria Spadola[2], Giuseppe Giuffrè[1] and Giovanni Tuccari[1]

[1]Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", Section of Anatomic Pathology, University of Messina, Messina 98123, Italy. [2]Department of Medical and Surgical Sciences and Advanced Technologies, G.F. Ingrassia, "Policlinico-Vittorio Emanuele", Anatomic Pathology Section, University of Catania, Catania, Italy.

Abstract

Malignant pleural mesothelioma (MPM) is a malignant tumour of the serosal membranes lining the pleural cavity, which has been linked with the occupational exposure to asbestos fibres; however, it rarely occurs in individuals not exposed to these fibres. In this regard, fluoroedenite (FE) fibres have been linked to increased mortality from pleural mesothelioma in Biancavilla, a town of eastern Sicily (Italy). These fibres are similar in size and morphology to amphibolic asbestos fibres and have been used as a building material for road paving and buildings in the town of Biancavilla and countries nearby. The aim of the present study was to investigate the immunohistochemical expression of Aquaporin 1 (AQP1) in a cohort of patients affected by MPM; taking into consideration its suggested independent prognostic role in asbestos related MPM, the possible correlation with clinicopathological parameters and patients outcomes was also evaluated.

Key words: Aquaporin 1, Malignant pleural mesothelioma, fluoroedenite, immunohistochemistry, prognosis

Introducing Memeber and Corresponding Author: Giovanni Tuccari - tuccari@unime.it

Introduction

Malignant pleural mesothelioma (MPM) is a malignant neoplasm of the serosal membranes lining the pleural cavity. The majority of cases are associated with occupational exposure to asbestos fibres; however, many other mineral fibres can cause mesothelioma [1,2]. Among these, fluoroedenite (FE) fibres have been linked to increased mortality from pleural mesothelioma in Biancavilla, a town of eastern Sicily (Italy) [3]. These FE fibres are similar in size and morphology to amphibolic asbestos fibres and have been used as a building material for road paving and buildings [4].

MPM has a very poor prognosis due to limited response to standard treatment and the median survival is approximately 6 to 12 months [5]. Many diagnostic biomarkers have been proposed in

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MPM such as calretinin, ck5, podoplanin, mesothelin, osteopontin and others [6,7], but unfortunately no available prognostic predictors are still clinically applied. The most important prognostic indicators for MPM include the histological subtype, sex and age at diagnosis [8]. Aquaporin 1 (AQP1) is a cell membrane channel with roles in water transport, cell motility, and proliferation. Given its function as a water channel, a role in pleural effusion fluid accumulation has been proposed [7]. Several studies highlighted the potential role of Aquaporin 1 (AQP1) as an independent prognostic factor for improved survival in MPM patients; in this regard, high levels of AQP1 immunohistochemical expression by >50% tumour cells were encountered in asbestos-related MPM and they predicted improved survival [9]. In the present study, we investigated the immunohistochemical expression of AQP1 in a cohort of patients affected by MPM FE-related living in Biancavilla. We also evaluated the correlation between immunohistochemical expression of AQP1 and clinicopathological parameters.

Materials and methods

Adequate bioptic tissue as well as cyto-inclusions from 8 patients who underwent surgery for MPM between 1996 and 2014 were retrospectively obtained from a larger series of 49 patients, of which clinico-pathological reports and follow-up data were available. All patients were resident in the town of Biancavilla or in nearby countries and showed evidence of environmental exposure to FE for many years. The histologic diagnosis of MPM and histologic subtypes were determined in accordance with World Health Organization (WHO) criteria. Immunohistochemistry for AQP1 was performed using the antibody: AQP1 (B-11, 1:100, Santa Cruz Biotechnology, Santa Cruz, CA, USA). AQP1 overexpression was defined when ≥ 50% of tumor cells showed membranous staining as previously reported [7]. The association between immunohistochemistry results and patient outcome was assessed by Fisher exact test. Kaplan-Meier analysis was performed for survival analysis. Cox Regression univariate and multivariate multivariate analysis were not conducted given the small number of cases. Statistical significance was defined as $p < 0.05$.

Results

The mean age of patients was 52 years (age range 50-93). Of 8 MPM patients, 4 were males and 4 were females. At the time of analysis, the mean follow-up value was 21.0 months (range 1,5 to 60 months); during this time, 7 patients showed tumor recurrence and died for the disease. Histologically, in accordance with WHO criteria, 4 cases were classified as epithelioid and 4 were biphasic subtypes. Immunohistochemical expression of AQP1 documented the immunoreaction linearly and circumferentially localized to membranes and not exclusively lining

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the apical cellular portion (Fig.1). The percentage score ranged from 0% to 100% and a score >50% was considered as clinically robust, similarly to that previously reported in the literature [7]. Utilizing this score, 5 cases showed AQP1 expression >50%, with a significant association (p = 0,021) of AQP1 overexpression with increased progression free survival (PFS).

Fig. 1 (A) Malignant epithelioid mesothelioma composed of solid nests and sheets of round cells with an epithelioid morphology (hematoxylin-eosin). (B) Immunohistochemical labeling for aquaporin 1 (AQP1) in the same case shows a linear, membrane-related staining in >50% of tumor cells. (C) Cell block from another case of epitheliod mesothelioma exhibiting aggregates of round epithelioid cells with hypercromatic nuclei and distinct nucleoli (haematoxylin-eosin) , with an evident linear and circumpherential immunoreactivity for AQP1 localized to cell membranes (D).

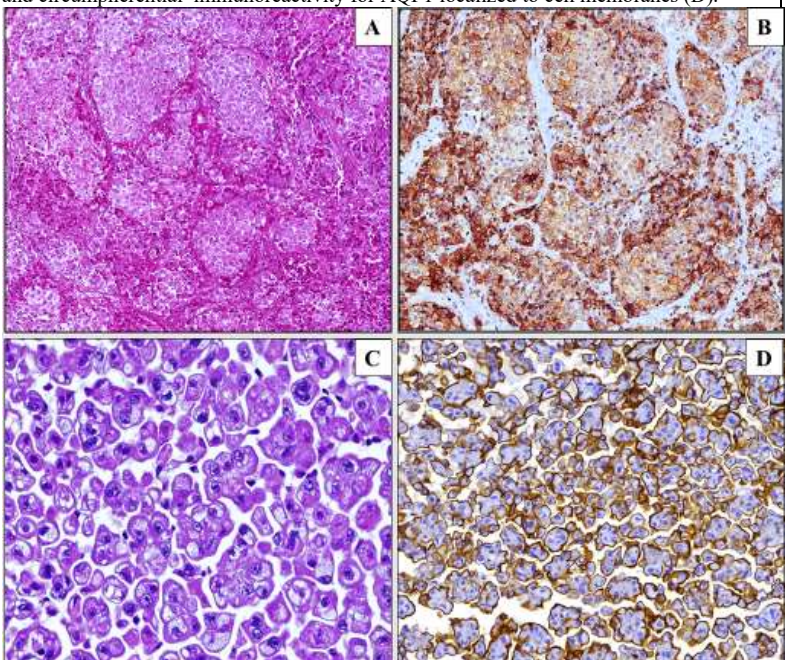
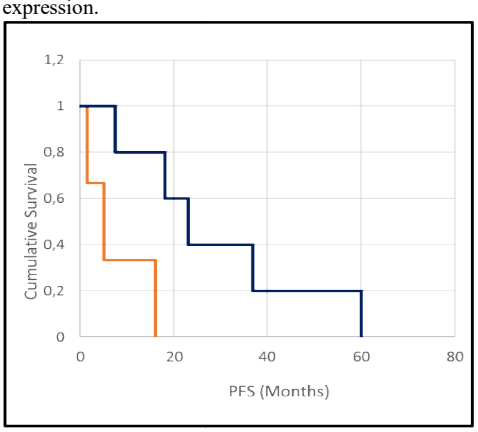


Fig. 2 Kaplan Meier curve of Aquaporin 1 (AQP1) expression in this cohort of 8 malignant mesothelioma patients. The median cumulative survival was 29,1 months for patients with > 50% AQP1 expression, versus a median cumulative survival of 7,5 months for patients with <50% AQP1 expression.



Of these patients, 4 showed a median PFS of 21 months and one patient is still alive with no tumor progression after a follow-up period of 5 years.

By contrast, patients with an AQP1 immunoexpression <50% showed a significantly shorter median PFS of 7,5 months (Fig. 2). No relationship emerged between AQP1 expression and other clinicopathological variables.

Discussion

FE fibres raised the attention of the scientific community due to an increase in the incidence of pleuric mesothelioma in the area of Biancavilla by an epidemiological survey conducted from 1988 to 1997 [10].

In the present study, we have started a systematic analysis of a cohort of MPM patients living nearby the area of Biancavilla. The AQP1 overexpression has been immunohistochemically revealed in 5/8 patents, which exhibited a significantly longer PFS in comparison to 3 patients who showed recurrences and worst prognosis. On the other hand, several reports highlighted that

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immunohistochemical overexpression of AQP1 in >50% tumor cells has been considered an independent predictor of longer survival in asbestos-related MPM [7,9]. In detail, also in our study, a significant association of AQP1 overexpression with increased survival was observed with a median PFS of 21 months for patients with ≥50% AQP1 expression versus a median PFS of only 8 months for patients with <50% AQP1 expression. In conclusion, our study represents the first report which emphasizes the immunohistochemical expression of APQ1 occurred in MPM related to environmental exposure to fluoroedenite fibres. We will continue our efforts in the already identified larger cohort to definitely establish the APQ1 prognostic significance.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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