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Spontaneous regression of malignant pleural mesothelioma: A case report

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Abstract
Malignant pleural mesothelioma (MPM) is a rare pleural disease with a poor prognosis. Currently treatment options are limited and the outcome is generally quite poor.
We report the case of a 76-year-old man diagnosed with locally advanced MPM who had partial spontaneous response for 2 years and remained asymptomatic for more than 3 years. The patient was taking specific herbal and vegetable diet during the course of response.
In our review of literature, a number of prognostic factors predict for better survival and response. However our patients did not have any of these factors. There have been reports of immune-induced responses in the literature. Our patient did indeed use some herbal products that might interfere with the immune system and explain his tumour regression and long period of disease stability. Further analyses and studies are needed in this setting to explore and identify specific immune pathways and targets to develop more effective treatment for MPM.

1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumour with a poor prognosis predominantly arising from the pleura. It is usually strongly associated with past exposure to asbestos [1]. Treatment options for patients with MPM include surgery, radiotherapy and/or chemotherapy [2,3]. Selected patients with favourable prognostic factors may benefit from surgery alone or in combination with chemotherapy and radiation therapy and could have a median survival of up to 2 years [4]. Prolonged disease-free periods are quite rare and only few cases of partial or complete spontaneous regression have been reported in the literature. A recent literature review could only find 5 reported cases of spontaneous regression of a primary thoracic malignancy [5]. MPM tumours are thought to be immunogenic based on animal studies and the good responses in some humans treated with immunotherapy. Some data reported suggest that spontaneous regression may be an immune-mediated phenomenon [6-8].

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2. Case presentation

We report the case of a 76-year-old gentleman diagnosed with an MPM. He has a history of hypertension, stage II chronic kidney disease and benign prostate hypertrophy. In addition he worked previously as a millwright with a high likelihood of occupational asbestos exposure and has smoked 5 pack-years but quit over 50 years ago.

He presented with mild intermittent pain in the left rib cage mostly on exertion, with no shortness of breath, fever or traumatic injury. The persistent pain prompted a chest X-ray, which at the time revealed no overt abnormalities. Two months later, due to non-resolution of symptoms, a CT of the chest was performed revealing asymmetric left pleural effusion and thickening (Figure 1a, b); further staging, including a CT of the abdomen+pelvis as well as a bone scan, did not reveal distant disease. An initial diagnostic and therapeutic thoracocentesis was positive for malignancy. The fluid contained groups of large cells in a background of acute and chronic inflammatory cells. Nuclear atypia with irregular nuclear membrane and frequent mitotic figures were seen. Immunostaining was positive for CK5/6, WT1, calretinin and negative for TTF1, CK20, CDX2, ER, BerEp4 suggestive of atypical mesothelial proliferation, favouring malignant mesothelioma. The complete blood work was normal. Of note the neutrophils to lymphocytes ratio (NLR) was 4.6. A confirmatory left pleural biopsy was also performed, revealing evidence of MPM (CK7 +, CK5/6+, TTF1−, CK20−, CD15−, CEA−, P63−).

Following the thoracocentesis, the patient became asymptomatic. His pulmonary tests were adequate. Although a trimodality approach (surgery, radiotherapy, and chemotherapy) was discussed, he was not deemed fit for surgery due to substantial risk of cardiovascular morbidity. Therefore, radiation and chemotherapy were discussed; however, the patient declined treatment and an active surveillance was initiated with close follow-ups including consults, physical exam and staging CTs every four to six months.

Beside his usual medications for hypertension, kidney disease, and prostate, the patient started taking various herbal supplements after his diagnosis. These included daily consumption of Chaga mushroom tea (one cup), a vegetable drink that consists of asparagus, kale, Italian parsley and watercress (one cup), Gyokuro green tea (one cup), selenium (200 mcg), vitamin C (2 g) and D (4000 units).

In the first year of surveillance, CT scans showed a mild progression in the pleural disease with no metastases in keeping with a stable disease as defined by the RECIST criteria version 1.1 (Figure 1c–f). The NLR was less than 3 during the 1st year then increased during the 2nd year (>4). Approximately two years after presentation, the pleural thickening/effusion surprisingly improved considerably and spontaneously (Figure 1g, h). This spontaneous regression lasted for a year with significant improvement in functional status. The NLR decreased at the same time approximately (<3). A regular follow up CT scan showed a mild progression of the thickening once again while the patient remained asymptomatic (Figure 1i, j). During the whole period of surveillance, the patient had an ECOG status of 0 and his daily consumption of the herbal products cited was consistent. Subsequently after 3 years of surveillance, the patient did progress on the CT Scan and became symptomatic; the NLR again increased (>4). He was started on Platinum agent/Pemetrexed combination.

3. Discussion

We present a case of a 76-year-old man with a confirmed MPM diagnosis that has spontaneous regression of his pleural disease and remains highly functional for three years without active medical treatment. The patient had a stable disease as defined by RECIST criteria during his surveillance after the first year followed by spontaneous partial response. Few cases have been reported in the literature regarding spontaneous remission of MPM and subsequent long survival without treatment. Allen et al., reported a case of a poorly differentiated epithelial mesothelioma that regressed spontaneously, with the disease remaining in remission for five years [9]. Other authors reported similar

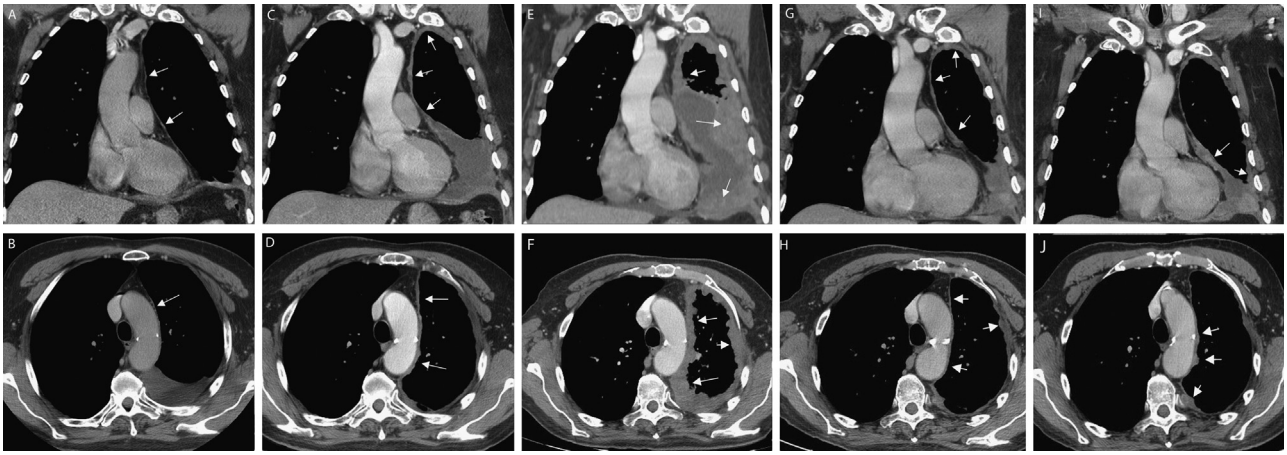

Figure 1 Chest CT images (coronal, upper row; axial, lower row). At presentation, subtle focal areas of left paramediastinal pleural thickening (arrows) and a small left pleural effusion were noted (a, b). Progression of disease was demonstrated in the 12 (c, d) and (e, f) 24-month follow up studies, with increasing pleural involvement (arrows) and pleural effusion. In the 30-month follow up, there was significant decrease of left pleural disease, consistent with spontaneous regression (g, h) (arrows). Six months after, mild progression of the pleural disease was noted again (i, j) (arrows).

cases of spontaneous regression and long survival [10,11]. In addition, Higashiyama et al., had reported a case of a stage IV epithelioid MPM patient that spontaneously regressed after a local relapse following a pleurectomy, but had recurred with slow growth after three years. This patient self-administered an oral mushroom extract and underwent a parasympathetic nerve stimulation therapy thought to provide potential immune-modulation, after which he experienced a high fever for two weeks with subsequent tumour regression [12].

Retrospective analyses have been used to determine a variety of prognostic factors in MPM potentially associated with prolonged survival. Microscopic features associated with long survival include innocuous nuclei, abundant cytoplasm as well as large numbers of small lymphocytes and scattered plasma cells [11,13]. MPM tumours of epithelioid type, age less than 60 years old and female gender were associated with a better prognosis in the German register [14]. High MIB-1 proliferation index (Ki67) was reported as a marker of worse prognosis [15]. Our patient did not have many of these positive prognostic factors (male gender, age greater than 60, microscopic features, Ki67 not reported) despite his long survival without any active treatment.

Furthermore, inflammation localised in the tumour has been reported as a possible immune-mediated mechanism of spontaneous regression. Thirty per cent of MPM patients exhibit serological or immune reactivity to MPM antigens [16]. The lymphohistiocytoid mesothelioma histologic subtype, known to have a better prognosis, is associated with marked lymphocytic and plasmacytic infiltrate [17]. Moreover, some mesothelioma antigens were reported to have disappeared or to be less expressed on relapse, an observation that is consistent with the immune reaction theory [11]. Current concepts of MPM biology suggests that the tumour is, to some extent, immunogenic [6] and clinical trials investigating immunomodulatory agents have shown evidence of response in a proportion of patients [7,8]. Lately, it was shown that PD-L1 is expressed in a substantial number of MPM patients and was associated with poor survival. With the development of drugs targeting PD-L1, this may be an important research avenue for these patients. On another hand, the NLR that reflects a systemic inflammatory response has been recognised as a poor prognostic marker in various cancers [18]. In our patient, the NLR was elevated at diagnosis and its level varied with the disease spontaneous response and progression. A mild inflammation was present and reported on the pathology favouring the immune-induced response hypothesis that might explain the prolonged stability of his disease and survival.

We acknowledge that our patient was on herbal products that might have played a role or interfered in stabilizing the disease or boosting the immune system against the tumour cells. Animal model and in vitro research demonstrated that curcumin might exhibit a variety of immunomodulating activities, including inhibition of growth and survival of T-lymphocytes, inhibition of antibody secretion by B-lymphocytes and inhibit the production of pro-inflammatory cytokines, including TNF-alpha and IL-1 [19,20]. Curcumin has also been shown in cell lines to inhibit NF-kB and FGF-2-induced angiogenesis to inhibit the proliferation of multiple cell lines [21,22]. Chaga has demonstrated antiproliferative effects in certain cancer cell lines [23], and potential stimulation of aspects of humoral immunity in in vitro studies [24]. Green tea contains numerous polyphenols and catechins, which have been shown to induce cell cycle arrest and apoptosis in many cancer cell lines [25], and inhibit the activity of certain tyrosine kinase receptors [26] (EGFR, HER2). Furthermore, it has been shown to decrease tumour growth and metastases in mice models [27]. However, such evidence cannot be extrapolated to human studies, and it is unknown how these herbal products may have affected the course of the patient's cancer.

An effective approach to investigate potential treatments for MPM would be identifying MPM antigens and targeting them with immune based therapies while overcoming the tumour's ability to evade the immune system. Currently, several trials are being conducted to investigate immunotherapy for the treatment of MPM, either as monotherapy or in conjunction with standard treatments (NCT01843374, NCT01265433, NCT01569919, NCT01583686).

4. Conclusion

In conclusion, spontaneous regression of MPM disease is a rare occurrence, as reflected by the few cases reported in the literature. It can be seen as a part of the spectrum of the natural history of the disease or part of the individual immune system targeting the tumour cells. Future research aimed to understand the underlying immune mechanism of MPM disease would help us develop more specific and potent therapies.

Conflict of interest

Sunil Verma reports serving on the advisory board of Roche, EISAI, Amgen, Novartis, Astra Zeneca. The rest of the co-authors have no conflict of interest to declare

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