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A case report of familial mesothelioma with bap1 mutation

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Abstract

Mesothelioma is a malignant neoplasm arising from the mesothelial surfaces, most commonly involving the pleura. We herein report a rare case of Familial Mesothelioma with BAP 1 mutation. The following Case report traces the course of the disease in a 40 years old female patient, including her initial presentation, Imaging studies, Histopathological & Immunohistochemistry findings, chemotherapeutic regimen used, response assessment and final outcome. It also touches upon the occurrence of the same malignant neoplasm in the above mentioned patient's mother a few months later, which eventually led to the identification of a very rare BAP 1 positive familial pattern of Mesothelioma.

Keywords

Mesothelioma; BAP 1; familial; asbestos; germline mutation.

Introduction

Mesothelioma is an insidious neoplasm that arises from mesothelial surfaces – pleural, peritoneum, tunica vaginalis or pericardium. The most common site involved is the pleura (60%–70%) followed by peritoneum (30%–35%), and pericardium (0.7%) [1]. Asbestos exposure is one of the most important causes for pleural and peritoneal mesothelioma worldwide with a latency of 30 to 40 years. It can be occupational or non-occupational. Apart from asbestos exposure, exposure to carbon nanotubes, radiation, viral oncogene (Simian virus 40) and other genetic factors have been associated with mesothelioma.

According to the Indian Council of Medical Research, National Cancer Registry Programme, the incidence is much lower in India accounting for 0.05–0.08 per 100,000 among men and 0.05–0.1 among women [1].

Familial mesothelioma is rare with no reports so far from India. Here we present a case of familial mesothelioma with BAP1 mutation.

Case Report

A 40 year old female from Northern India came with complaints of chest, shoulder & back pain with history recurrent pneumothorax for which pleurodesis had been done earlier at her hometown. On evaluation, the PET CT showed hyper metabolic peritoneal and pleural deposits with paraaortic lymphadenopathy, low grade pleural effusion and minimal ascites.

Upper GI scopy and Colonoscopy were normal. CT guided biopsy from the left para aortic node was suggestive of epithelioid mesothelioma. She was a home maker and had no history of asbestos exposure.

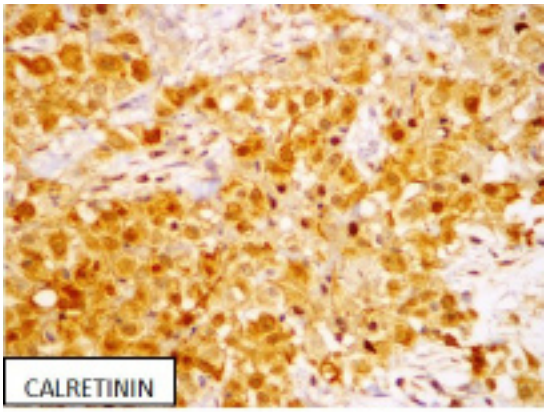

Figure 1: IHC for calretinin

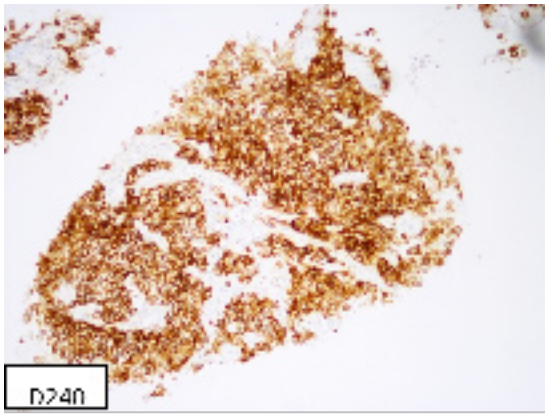

Figure 2: IHC for D240

She was started on palliative chemotherapy with Pemetrexed and Cisplatin and had a stormy course in the hospital, requiring ICU support for sepsis and respiratory failure. She improved in between and completed 3 cycles of chemotherapy. The interim PET CT after 3 cycles showed partial response to therapy.

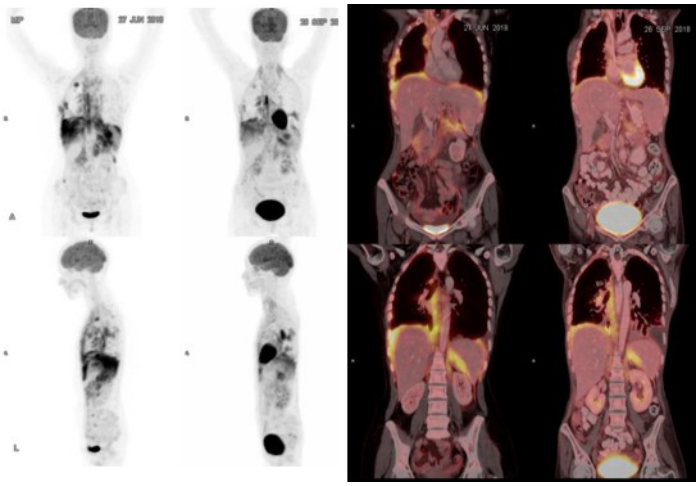

Figure 3: Interim PET CT – partial response

In view of her poor general condition she was continued on supportive care, TPN and further chemotherapy was withheld.

She continued to deteriorate with new onset pneumonic consolidation and sepsis requiring ventilator support. Her condition worsened and she expired in the November of 2018.

After a few months, her mother presented with complaints of abdominal distension and chest pain. On evaluation, PET CT showed hypermetabolic peritoneal and pleural deposits with nodal secondaries. Pleural biopsy was suggestive of mesothelioma. Considering the strong family history in her daughter, we planned for genetic analysis. The hereditary gene panel was suggestive of BAP1c.306C>G (p.Asn102Lys) (exon 5) and SDHC mutation (intron 2) c.78-1G>A (splice variant) positive.

We advised her palliative chemotherapy but the family wanted to travel back hometown for personal reasons and was lost for follow up.

Discussion

Mesothelioma is a malignant neoplasm arising from the mesothelial surfaces of the pleura, peritoneum, tunica vaginalis or pericardium. Eighty percent of mesotheliomas are of pleural origin with 70% associated with asbestos exposure.

In some villages in Greece, Turkey and Bulgaria, the soil levels of asbestos is very high. Inhalation of other fibrous silicates, such as erionite, has also been implicated as a potential cause of malignant pleural mesothelioma, as shown in epidemiologic studies of a region in Turkey (Cappadocia), which show an abnormally high incidence of pleural mesothelioma [2].

Approximately 12% of malignant mesothelioma is associated with germline mutations. This number is very similar to those seen with other solid malignancies like ovary, colon and prostate. Of this, BAP1 mutation contributes to one third of familial mesotheliomas. Other genes that are associated with mesothelioma include, TMEM127, CHEK2, MRE11A, VHL, WT1, CDKN2A, BRCA2 and SDHA [3]. Six of the genes with germline mutations—BAP1, vBRCA1, BRCA2, CHEK2, ATM, and MRE11A— have a well established role in the HR DNA repair pathway Few characteristics can predict the possibility of a germline etiology – lack of asbestos exposure, younger age of onset and presence of second malignancies [3].

BAP1, located on chromosome 3, regulates key histones and transcription factors associated with tumor development. It functions as a tumor suppressor gene. Loss of BAP1 is associated with a familial cancer syndrome that also includes uveal melanoma, cutaneous melanoma and other malignancies. [4,5]. BAP1 mutations are more common in epithelial than sarcomatous or biphasic mesothelioma[8].

BAP1 mutation is also seen in 25% of sporadic cases [8]. The discovery of a susceptibility gene might help in classifying the high and low risk population.

The role of genetic factors was explored in Turkey, where exposure to erionite was associated with mesothelioma in six successive generations. This showed the exposure to erionite, a well known causative factor for malignant mesothelioma, was only a supportive factor in already genetically predisposed individuals [9].

Mesothelioma is rare in Indian population. Familial mesothelioma is a rare entity and so far no clusters have been reported in India. The incidence of mesothelioma is around 0.05–0.08 per 100,000 among

men and 0.05–0.1 among women. In view of the strange presentation, with the mother also presenting with the same diagnosis, the genetic analysis was done. The BAP1 mutation detected in this panel is classified as of uncertain significance in view of lack of literature support.

First line treatment options include pemetrexed and platinum combinations. Maintenance pemetrexed can be continued on extrapolation from NSCLC data. If the disease progresses more than 6 months after first line platinum based combination, re-challenge with pemetrexed and platinum can be considered. If the time to progression is less than 6 months, single agent chemotherapy with gemcitabine, vinca alkaloids or anthracyclines can be considered.

Anti PD1 and PDL1 are also viable options. In a preliminary phase III study pembrolizumab had better ORR when compared to gemcitabine and vinorelbine combination, but PFS and OS were similar between both the groups We still lack randomized data to support the use of immunotherapy in mesothelioma.

Conclusion

Mesothelioma is rare in India, with the first case being reported in 2015. Data on the prevalence of familial mesothelioma and the associated mutations in Indian population is lacking.

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