Is there a role of immunosenescence in the pathogenesis of malignant mesothelioma? A case study

Sir,

Malignant pleural mesothelioma is the most common cause of primary pleural malignancy. Approximately, 35% of effusions associated with it are described to be inflammatory/reactive/lymphocytic in nature.[1] The latency period, defined as the time between the first exposure to asbestos and the development of mesothelioma, has been reported to be 40 years on an average. However, latency periods as long as 72 years have been documented.[2]

Here, we present an interesting case of malignant mesothelioma in a 90-year-old female with a remote and minimal history of exposure to asbestos. The case is quite interesting because this is one of the longest latency periods ever reported.

A 90-year-old female with a history of bronchiectasis and chronic pseudomonas infection, prior Mycobacterium avium intracellulare infection, pulmonary arterial hypertension, and atrial fibrillation was seen in the clinic for increasing shortness of breath over a period of 5 days. A chest X-ray revealed a large left-sided pleural effusion that was considerably larger in size compared to 8 months back. A thoracentesis was performed after admission which revealed yellow colored hazy fluid. A total of 1200 cc of pleural fluid was aspirated from the left pleural space under ultrasound guidance. The fluid analysis revealed a lymphocyte predominant exudative fluid [Table 1]. The differential diagnosis for the lymphocyte predominant fluid is narrow and includes the following-Tuberculosis, sarcoidosis, lymphoma, yellow nail syndrome, chylothorax, and rheumatoid pleurisy. Flow cytometry was performed which excluded lymphoma and demonstrated a CD4 to CD8 ratio of 12:1. The clinical picture and result of the fluid analysis excluded chylothorax, yellow nail syndrome, and rheumatoid arthritis as possible causes. Further immune-histochemical evaluation of the pleural fluid revealed cells that were positive for Calretinin and CD68, and negative for Ber-EP4, supporting a reactive process. Malignant cells were not encountered. Post-procedure computed tomography scans revealed a small hydropneumothorax, and to our surprise, multiple left-sided pleural-based soft tissue masses [Figures 1 and 2]. A single chest wall implant was also noted. A transthoracic needle biopsy from the mass was performed, followed by a small-bore indwelling pleural catheter catheter placement. It demonstrated large epithelioid tumor cells in cords, nests and tubular glandular structures [Figure 3]. These tumor cells were immunoreactive for cytokeratin AE1/AE3, calretinin, cytokeratin 5/6, WT1, D2-40 [Figure 4] and negative for thyroid transcription factor-1, and Napsin A. This immunoreactive pattern was consistent with mesothelioma. A nonaggressive course of treatment, focusing on comfort care was preferred by the patient. A more detailed history, obtained after this rather unexpected diagnosis, revealed that the patient was employed as a messenger at naval yard in 1940s about 74 years back. Any further exposure to asbestos was ruled out.

Table 1: Results of pleural fluid analysis

| Pleural fluid                  | Value         |
|-------------------------------|---------------|
| WBC                            | 4800/cmm      |
| Differential count             | 1% N, 85% L, 14% mesothelial |
| Pleural protein/serum protein  | 4.5/6.2       |
| Pleural glucose                | 107 mg %      |
| Pleural chylomicron            | Negative      |
| Pleural fluid LDH/serum LDH    | 473/252       |
| Pleural fluid pH               | 7.41          |
| Pleural fluid culture          | Negative      |
| Pleural fluid RBC              | 9900/cmm      |

WBC: White blood cell, RBC: Red blood cell, LDH: Lactate dehydrogenase

Figure 1: Coronal view demonstrating left pleural based multiple masses. A large left pneumothorax is seen

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out. Based on this history of rather indirect exposure to asbestos, and that too with a long latent period of >70 years, we felt that it would be worthwhile to review the cause-and-effect relationship between asbestos and mesothelioma.

One explanation for such a long latency period could be that minimal exposure to asbestos resulting in delayed development of cancer. It is also interesting to note that mesothelioma can occur among immunocompromised people even without any history of exposure to asbestos.

We feel that age-related frailty of the immune system might explain the development of mesothelioma in her case. Lending support to this hypothesis would be the absence of pleural plaques/calcifications.

We reviewed some of the principal concepts of tumorigenesis associated with asbestos exposure. Even though the available data is unclear, the intensity of exposure and latency periods are commonly assumed to be inversely related in those who develop cancer.\(^3,4\) The risk of cancer development is related to the intensity of exposure. The duration of exposure, even though considered to be less important, is also related to the risk of cancer.\(^5\) Thus, chronic low-level exposure can account for the development of cancer. It is postulated that cancer will develop when the exposure to asbestos has reached a certain degree, which varies between individuals.\(^6\) It is also thought that the failure of the body’s immunological surveillance system to detect and kill cancer cells results in the development of cancer.\(^6\) The reports of mesothelioma being related to HIV/AIDS, simian virus 40 infection, organ transplant, or advanced age lends credence to the theory.\(^5\)

Cancer is the result of the interplay of multiple factors: Exposure to asbestos as well as the way the immune system responds to it. Considering the low-degree of exposure and development of cancer after such a long period, this case provides support for the role of immunosenescence in the development of mesothelioma.

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Young onset hemoptysis: A rare cause of pulmonary arterial aneurysm

Sir,

A 19-year-old gentleman from Tamil Nadu, presented to us with complaints of cough and mild-to-moderate hemoptysis for four months and dyspnea on exertion (grade 1 Modified Medical Research Council) over the past two months. It was not associated with fever, chest pain, loss of weight or loss of appetite.

There has been no history of joint pain, skin rashes, oral ulcers, claudication pain, diminution of vision, double vision or hoarseness of voice. He does not have any other comorbidity and has no addictions.

His vitals were stable on presentation. Peripheral pulses were well felt. General examination was within normal limits. There were no signs suggestive of uveitis, and there were no skin rashes or skin discoloration. Systemic examinations were also within normal limits.

His total blood count was elevated (12,300 cells/mm³) with neutrophilic predominance. X-ray of the chest showed right hilar prominence [Figure 1]. His sputum examinations were negative for acid fast bacilli (AFB) on direct smear and culture. Polymerase chain reaction (PCR) for Mycobacterium tuberculosis was also negative, but bacterial culture grew Haemophilus Parainfluenzae, which was treated with antibiotics. Computed tomography (CT) of the thorax with a pulmonary angiogram, which was done as part of hemoptysis evaluation, showed multiple segmental pulmonary artery aneurysms with filling defects - thrombus [Figure 2], consolidation in the right middle lobe and ground glass opacities in the right middle and lower lobes – which likely represented alveolar hemorrhage. On further evaluation, a venereal disease research laboratory test was negative and other bacterial and fungal infections were ruled out. The vasculitis workup was negative. Clinical screening for Marfan syndrome was negative. Echocardiography was done, which ruled out any cardiac anomaly and pulmonary hypertension. Thus, the differential diagnosis was narrowed down to Bechet's disease and Hughes Stovin syndrome.

He did not have oral or genital ulcers. His fundus examination ruled out uveitis and the pathergy test was negative. HLA B-51 analysis was also negative. An ultrasound Doppler screening of both the lower limbs was negative for any deep venous thrombosis. Thus, a diagnosis of Hughes Stovin Syndrome was made. He was started on pulse steroid and later on Mycophenolate Mofetil and tapering doses of steroids.

Hughes Stovin syndrome (HSS) is a rare autoimmune disorder, first described by John Patterson Hughes and Peter George Ingle Stovin, two British physicians, in 1959.[1] It is characterized by pulmonary artery aneurysms and deep vein thrombosis, it can present with recurrent fever, cough,