

## **EDITORIAL**

# **Malignant pleural effusion: would the real cause please stand up?**

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Pleural effusions in patients with malignant disease are not invariably due to metastatic spread to the pleura and thus, they are not always incurable. For example, about 5% of patients with effusions due to lung cancer have subsequently been found to be operable and curable [1]. It is, therefore, important to assess the potential curability in all cancer patients with cytologically negative effusions, since they may not only be free from pleural metastases but also from tumour spread elsewhere.

On the other hand, autopsy studies indicate that only about 55-60% of patients with proven pleural metastases develop pleural effusions. What are the mechanisms that cause the development of an effusion in one patient with malignant involvement of the pleura and what prevents it in another?

In this issue of the Journal, SAHN [2] suggests that neoplastic involvement of the lymphatic drainage system, either in the parietal pleura and/or in the mediastinum, is the primary mechanism by which pleural metastases cause pleural effusions. This leads to accumulation of the fluid which normally leaves the pleural space. These conclusions are based primarily on postmortem studies in which the presence of pleural effusions was correlated with the autopsy findings [3, 4]. If the lymphatic clearance is normal, excess fluid that enters the pleural space can usually be removed, since the maximum capacity of the lymphatics for fluid removal is up to 25 times the normal rate of fluid formation [5]. Therefore, unless the amount of pleural fluid being formed is very high, pleural fluid will accumulate only if there is also decreased lymphatic clearance. Indeed, it has been shown that the clearance of fluid from the pleural space is decreased in patients with malignant pleural effusions [6].

However, there are several observations that seem to be incompatible with the theory that lymphatic obstruction is solely responsible for the pleural fluid accumulation.

Firstly, malignant pleural effusions are exudates. If the pleural effusion developed solely as a consequence of lymphatic obstruction, one would anticipate that the fluid would be a transudate, since the fluid that normally enters the pleural space is a low-protein ultrafiltrate from the parietal side [7-9].

Secondly, the rate of pleural fluid formation, at least

in some patients, is much too high to be explained on the basis of lymphatic obstruction. If data in sheep can be extrapolated to humans, the normal rate of pleural fluid formation is about 0.01 mL·kg<sup>-1</sup>·h<sup>-1</sup> [10]. In a 60 kg individual, only about 15 mL of pleural fluid would accumulate during each 24 h with complete lymphatic obstruction. In the clinical arena, many patients with malignant pleural effusions have pleural fluid accumulation rates many times greater than this. After patients with malignant pleural effusions have chest tubes inserted and the hemithorax drained, it is common for the fluid egress to exceed 100 mL·day<sup>-1</sup>.

Thirdly, if the accumulation of pleural fluid was due solely to lymphatic obstruction, why are malignant cells found in more than 90% of effusions [12], and why are so many malignant effusions bloody? A possible explanation for the high rate of positive cytology is the invasion of the parietal pleura by the metastatic tumour as it obstructs the lacunae of the lymphatics. However, it has been shown that many patients have effusions only when their visceral pleura is involved [3, 11, 12]. The visceral involvement probably represents blood-borne metastases from the primary tumour and leads to secondary spread across the pleural space to the parietal side. However, given that severe visceral and parietal involvement is usually observed in malignant pleural effusions, why should this not be an important cause of pathological fluid formation in itself?

We believe (although we have no direct proof) that increased pleural fluid formation contributes significantly to the development of a malignant pleural effusion. There are several possible explanations for this. The presence of pleural metastases may increase the permeability of the capillaries in the visceral and/or parietal pleura. This would also explain why malignant effusions are exudates. Further, the presence of a primary tumour or metastases in the lung may increase the amount of interstitial fluid, which would then add to increased pleural fluid formation. Finally, the presence of mediastinal lymph node involvement might decrease lymphatic flow from the lung and lead to increased amounts of fluid entering the pleural space by traversing the visceral pleura.

We suggest that pleural fluid accumulates due to the combination of both increased pleural fluid formation and a decreased capacity of the lymphatics to remove fluid. Only the combination of these two mechanisms gives us an answer to some of the theoretical problems that we have with the one single hypothesis, and this formulation may also better explain why some patients with pleural metastases have malignant effusions while others do not.

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