ARTICLES FOR DISCUSSION


The authors identified 4 patients who underwent bone marrow transplantation and subsequently developed pleuroparenchymal fibroelastosis. The details of the patients are shown below.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>Age (years)</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>Aplastic anaemia</td>
<td>Acute myeloid leukaemia</td>
<td>Acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>Bone marrow transplantation conditioning procedure</td>
<td>Cyclophosphamide</td>
<td>Total body irradiation</td>
<td>Total body irradiation</td>
</tr>
<tr>
<td>Transplant type</td>
<td>Allogenic, matched sibling</td>
<td>Allogenic, sibling</td>
<td>Allogenic, sibling</td>
</tr>
<tr>
<td>Time from bone marrow transplantation to presentation (in years)</td>
<td>2 years 9 months</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Dyspnoea, chest pain</td>
<td>Dyspnoea, phlegm, weight loss</td>
<td>Dyspnoea, bronchitis</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Bilateral</td>
<td>Right</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Extra-pulmonary graft vs host disease</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CT</td>
<td>Patchy visceral pleural thickening</td>
<td>Visceral pleural thickening</td>
<td>Non-uniform visceral pleural thickening</td>
</tr>
<tr>
<td></td>
<td>Subpleural blebs</td>
<td>Pleuroparenchymal tags</td>
<td>Subpleural blebs</td>
</tr>
<tr>
<td>Pathology</td>
<td>Mosaicism</td>
<td>Mosaicism</td>
<td>Mosaicism</td>
</tr>
<tr>
<td>Method of sampling</td>
<td>Video-assisted thoracoscopic biopsy</td>
<td>Postmortem</td>
<td>Video-assisted thoracoscopic biopsy</td>
</tr>
<tr>
<td>Pleuroparenchymal fibroelastosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Progressive disease</td>
<td>Died 12 years after bone marrow transplantation</td>
<td>Stable disease</td>
</tr>
</tbody>
</table>

There were a wide variety of ages. While the bone marrow transplant conditioning procedure (and associated drugs and radiation) are mentioned, there are no details regarding any prior chemotherapy that the patients may have received. Late effects of a drug obviously are in the differential as discussed below.

In 2 cases a specific upper lobe distribution is mentioned, whereas in 2 it is not so clear and in 1 the CT was described as showing a perihilar reticular pattern.
Interestingly all patients presented with recurrent pneumothoraces and also showed histologic evidence of obliterative bronchiolitis/constrictive bronchiolitis.

The authors note that the etiology of pleuroparenchymal fibrosis in this groups of patients is unknown and possible causes include drugs, radiation, and graft versus host disease. Late effects of idiopathic pneumonia syndrome were also considered.

Comment:

This is a small case series that I thought was of interest in idiopathic pleuroparenchymal fibroelastosis.

The association of fibroelastosis is of interest because of previous cases reported as drug reactions such as one from Mayo Arizona entitled “Upper lobe pulmonary fibrosis associated with high dose chemotherapy containing BCNU for bone marrow transplantation” (Mayo Clin Proc 2003;78:630). That patient also had pneumothoraces and likely has the same thing described by these authors but at the time a drug was implicated. One wonders how many putative cases of drug fibrosis might actually represent this condition.

Another reason to discuss this paper was the recent recognition of fibroelastosis as something to be distinguished from “regular fibrosis.” In some cases we diagnose UIP (and hence IPF) in which the scarring is associated with appreciable elastosis and perhaps we will have to pay more attention to the exact type of fibrosis. It would be of interest to hear what our Japanese colleagues say about this since they have been using elastic tissue staining for non-neoplastic lung disease for many years.

886 resected pulmonary adenocarcinomas were studied.

Three micropapillary patterns were identified: papillary tufts without fibrovascular core lying freely within alveolar spaces, papillary tufts lying in clefts or spaces within fibrous tissue, and micropapillary tufts floating within cystic spaces lined by tumor cells.

The percentage of micropapillary change was defined as none, focal (1-5%), moderate (5-50%), and extensive (≥ 50%). All of those in the last group were studied for EGFR and K-ras mutations.

The cases appear to have been classified according to the 2004 WHO classification for adenocarcinoma (BAC, acinar, papillary, solid with mucin, and mixed).

No tumors showing a pure micropapillary pattern were encountered. A micropapillary pattern was found in all of the major subtypes of adenocarcinoma studied.

Carcinomas containing a micropapillary pattern showed strong staining for E-Cadherin and beta Catenin. MUC-1 was also strongly expressed.

EGFR mutations by mutational analysis, were found in 37 of the 66 cases with an extensive micropapillary pattern (56%). KRAS mutations were found in 4 of the 66 cases. Similar mutations for EGFR and KRAS were found when micropapillary regions were compared with non-micropapillary regions.

The extent of micropapillary change has prognostic significance for a number of findings including lymph node metastases, lymphatic invasion, venous invasion, and stage as shown in Table 1 below. Smoking was a significantly more frequent finding in tumors with a micropapillary pattern.

Not surprisingly very similar findings were noted when micropapillary positive versus micropapillary negative tumors were compared. The presence of a micropapillary pattern had an unfavorable affect on lymph node metastases, pleural invasion, lymphatic invasion, venous invasion, and staging.
The effect of survival of micropapillary patterns shown in the two graphs below.

Comment: A very large and meticulous study that appears to confirm a number of prior studies on the micropapillary pattern in lung adenocarcinoma. The authors found 28% of their adenocarcinomas had micropapillary regions comprising greater than 1% of the tumor. Previous studies have suggested anywhere from 11% to 50% frequency of micropapillary pattern so there may be some definitional issues that vary or there may be geographic/ethnic differences.

The authors describe the lung findings in 5 patients with Marfan syndrome.

Background: Approximately 25% of patients with Marfan’s have de novo mutations and the remainder are familial. Mutations are found in the FBN1 gene on chromosome 15 which encodes the connective protein Fibrillin-1. Prior literature has noted that appreciable numbers of patients with Marfan’s syndrome have some underlying pulmonary pathology. Previously reported changes include: cystic spaces, emphysema, spontaneous pneumothorax, focal pneumonia, bronchiectasis, bullae, congenital pulmonary malformations, particularly middle lobe hypoplasia, and apical fibrosis.

The authors studied 3 men and 2 women with an age range of 18 to 50. Three had had cardiac surgery and died and autopsy tissue was evaluated. The remaining 2 patients had pulmonary symptomatology including COPD and recurrent pneumothorax. Autopsy tissue was available in 3 cases and there one case each with explant and wedge biopsy.

Pulmonary specimens from all cases were described as showing “distal acinar emphysema.” Some cases had septal scarring. One case had concomitant centrilobular emphysema. Additional nonspecific changes included pneumonia, congestion, pleural adhesions, hemorrhage, and pleuritis. The pathology of the 5 cases is illustrated below.
The authors then discussed the differential diagnosis in a pictorial form which includes classic centrilobular emphysema, classic panacinar emphysema, interstitial emphysema (interstitial air), paracitictricial emphysema, and LAM (shown below).

Comment: I am not sure I would characterize all those images as distal acinar emphysema. I will be interested to hear what others say about them. There does not appear to be anything specific about this change and other causes of “holes” in the lung would remain in the differential including Birt-Hogg Dube, smoking, etc. The only way I would recognize the change as Marfan’s syndrome would be to know that the patient had Marfan’s.
ARTICLES FOR NOTATION

1) Non-neoplastic Disease

1. Bayram H and Ghio AJ. Killer jeans and silicosis (Am J Respir Crit Care Med 184:1322, 2011). An editorial comment on a recent epidemic of silicosis that has been noted in individuals involved in sandblasting jeans in order to get the appropriate “look.” References to several of the recent articles on that epidemic are included in the editorial.

2. Hayashi T, et al. Prevalence of uterine and adnexal involvement in pulmonary LAM: a clinicopathologic study of 10 patients (Am J Surg Pathol 35:1776, 2011). In a study of uteri from 10 patients with pulmonary LAM, nine were found to have uterine involvement, much higher than has been previously appreciated. All patients had associated involvement of retroperitoneal or pelvic lymph nodes. Patients with TSC-LAM as well as patients with sporadic LAM showed uterine involvement and they noted more prominence of epithelioid-shaped LAM cells in the former. The authors postulate that the uterus or an adjacent locale could conceivably be the primary site of origin of LAM.

3. Kavuru MS, et al. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis (Eur Respir J 38:1361, 2011). An open-label phase II trial of rituximab in 10 patients with PAP. There was improvement in arterial blood oxygenation, lung function and HRCT as well as a reduction in anti-GM-CSF levels. The findings suggest that the disease pathogenesis is related to autoantibody levels.

4. Paris C, et al. Giant cell interstitial pneumonia: report of two cases with high titanium concentration in the lung (Am J Respir Crit Care Med 184:1315, 2011). The authors describe two patients with GIP who had no evidence of tungsten carbide or cobalt exposure. Both had high titanium levels and titanium was postulated as the causative agent. It was noted that in studies of GIP in the past, high amounts of titanium have been commonly found (in addition to cobalt or tungsten carbide).

5. Parisinos CA, et al. Sarcoidosis complicating treatment with natalizumab for Crohn’s disease (Thorax 66:1109, 2011). Two patients presented who appeared to develop sarcoidosis after treatment with natalizumab. Both had underlying Crohn’s disease. Both patients had a complicated clinical course and were on a number of other drugs and the authors’ conclusion regarding an association is not unreasonable although it would be very difficult to fully prove given the complicated aspects of both cases.

Aside: I think there are a lot of reports in the literature of “sarcoid” complicating various drugs but what in fact their reports of are a granulomatous reaction and whether or not the patients had good clinical-radiologic-pathologic sarcoid is often not addressed.

7. Lee JS, et al. Gastroesophageal reflux therapy is associated with longer survival in patients with IPF (Am J Respir Crit Care Med 184:1390, 2011). A retrospective regression analysis of 204 patients with IPF looking at those who reported symptoms of GER, those with a history of GER, those who used GER medications, and those who had had Nissen fundoplication. The use of GER medications was an independent predictor of longer survival time and was associated with a lower radiologic score. The authors state that “these findings further support the hypothesis that GER and chronic microaspiration may play important roles in the pathobiology of IPF”.

2) Neoplastic Disease

1. Churg A, et al. The fake fat phenomenon in organizing pleuritis: a source of confusion with desmoplastic malignant mesotheliomas (AJSP 35:1823, 2011). A series of 9 cases from the US-Canadian Mesothelioma Panel. All were finally interpreted as fibrous pleurisy that had shown fat-like spaces that could be/had been confused with adipose tissue (and hence mesothelioma with invasion of the process into adipose tissue). A horizontal orientation of keratin-positive spindle cells was noted in these cases in contrast to the downward growing spindle cells between clearly definable fat cells in desmoplastic mesothelioma.


   a. Stage I tumors it was shown that moderate to poorly differentiated histology, vascular invasion, and visceral pleural invasion were independent risk factors for recurrence.
   b. Stage II tumors adenocarcinoma histology and visceral pleural invasion were risk factors for recurrence.

   [Visceral pleural invasion is not defined or referenced but the authors state they used the seventh edition of the TNM and thus visceral pleural invasion would be PL1 or PL2.]

4. Nagy-Mignotte H, et al. Primary lung adenocarcinoma: characteristics by smoking habit and sex (ERJ 38:1412, 2011). A retrospective review of 848 patients diagnosed with adenocarcinoma of the lung and with documented smoking status. The authors found differences when patients were stratified according to sex and smoking history. Female smokers were significantly younger than female never-smokers; whereas, in males smoking did not influence findings of presentation. Male current smokers were significantly older than female current smokers.