 Companion Meeting  
Friday May 31  

Lung  
Room 102 / 11:15 - 1:00 pm  

Convenor  
A/Prof. Wendy Cooper  
Royal Prince Alfred Hospital, Sydney, NSW.  

Lecture:  
Dr Edwina Duhig,  
Sullivan & Nicolaides Pathology, Gold Coast, QLD:  
“Liebow’s contribution to pulmonary pathology”.  

Case 1:  
Dr Andrew Dettrick,  
The Prince Charles Hospital, Brisbane, QLD.  

Case 2:  
Dr Georgina England and A/Prof. Sonja Klebe,  
SA Pathology, Adelaide, SA.  

Case 3:  
Dr Tristan Dodds,  
Royal North Shore Hospital, Sydney, NSW.  

Case 4:  
Dr Kenneth Lee,  
Concord Repatriation General Hospital, Sydney, NSW.  

Case 5:  
Dr Min Ru Qiu,  
SydPATH, St Vincents Hospital, Sydney, NSW.  

Case 6:  
Dr Nicola Kingston,  
Auckland Hospital, Auckland, NZ.
The Legacy of Averill A Liebow

Dr EE Duhig

Sullivan Nicolaides Pathology, John Flynn Hospital, Tugun, QLD 4224.

In 1960, Averill Abraham Liebow was the author of the seminal paper describing bronchiolo-alveolar carcinoma\(^1\). He wrote it following an international consensus meeting and drew together a group of tumours previously called “bronchiolar cell carcinomas”, “alveolar cell tumours” and “pulmonary adenomatosis”. This tumour was defined as a “well differentiated adenocarcinoma, primarily in the periphery of the lung beyond a grossly recognisable bronchus with a tendency to spread chiefly within the confines of the lung by aerogenous and lymphatic routes, the walls of distal airspaces often acting as supporting stroma for the neoplastic cells.” While trying to sell the concept, he acknowledged there was little objection to applying the term although there was not unanimous agreement in relation to the details. He went on to confess that it would be questioned how to differentiate “ordinary” adenocarcinoma from BAC and that at that time he felt the distinction couldn’t be made. It is not surprising, given this statement that it took until the 1999 WHO classification for a strict definition to be applied. Even then, the criteria were variably applied and, in the IASLC 2011 classification, this term was abandoned.

He emigrated from Austria as a child and went on to graduate head of his year at College of the City of New York before receiving his medical degree from Yale University. Following university he went on to study pathology and became a member of faculty at Yale where he stayed until 1968. From 1968 to 1975 he was professor at the University of California at San Diego\(^2\).

During World War II he served in the Yale Medical Unit in the South Pacific and at the end, he was a member of the Atomic Bomb Casualty Commission that surveyed the aftermath of the Hiroshima and Nagasaki bombs. In one of his earliest papers, he published a detailed account of injuries sustained in the blasts\(^3\). In this paper he noted, less than 5% of those directly exposed within 1200 yards of ground zero were survivors, few survivors had “severe” injuries and amongst survivors an incidence of fractures of only 4.5% was recorded.

Following the war he settled back into his career. He ultimately was uniquely placed to contribute to the development of pulmonary pathology. His consultation files drew on an enormous referral base, a reflection of his huge intellect and the respect his colleagues held him in. For example in some of his later publications he with co-authors described
lymphomatoid granulomatosis\textsuperscript{4, 5}(LyG). The initial publication drew on 36 cases from his file while the subsequent paper included all 152 file cases including an Australian case.

While not all his concepts have stood the test of time, Averill Liebow could be described as the father of pulmonary pathology. He wrote papers on benign and malignant lung disease, on biopsy and cytology material and on anatomy. He was the author of the 1952 AFIP fascicle on lung tumors and in this publication, he sought not to approach carcinomas from a purely anatomic point of view but noted “For convenience, malignant epithelial bronchogenic tumors of the lung will be classified on the simplest possible histologic basis: 1. Epidermoid carcinoma 2. Anaplastic carcinoma 3. Adenocarcinoma 4. Mixed forms...of the preceding types.”\textsuperscript{6} The interstitial pneumonias had been recognised for many years but in 1969 he and Charles Carrington were the first to classify them into usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans interstitial pneumonia (BIP) and giant cell interstitial pneumonia (GIP)\textsuperscript{7}.

LyG is one that has stood the test of time and many of his suppositions in relation to this disease have been borne out. He and his co-authors considered it, despite similarities, a separate entity to Wegener’s granulomatosis, they noted a predisposition in the immunosuppressed and, subsequently, the transplant population and they raised the possibility of altered immune reactivity and gave possible examples of causes, amongst these being EBV\textsuperscript{5}.

Alveolar proteinosis was another condition he and co-authors described\textsuperscript{8}. While there have been advances in the understanding of alveolar proteinosis, the basic premise that they first described in 1958 is also still relevant. Over a period of five years the authors had encountered a disease in which there was filling of alveolar spaces by PAS positive proteinaceous material that was rich in lipid. They considered the material to be produced by the alveolar lining cells that sloughed into the lumen, became necrotic and yielded granules and laminated bodies to the alveolar content. They came to this conclusion probably without fully knowing the role of surfactant, which around this time was being described and certainly were unable to recognise that there was a defect in macrophage function. In retrospect, it was important that they recognised this unusual condition. In their series, eight of the 27 subjects died of their disease. Today, given the understanding of the pathogenesis and advances in therapy, it seems unthinkable that this condition would be associated with a mortality of just under 30%.

Other conditions that he was an author of a paper included IVBAT (now recognised as epithelioid haemangioendothelioma), eosinophilic granuloma, hyalinising granuloma, lymphangiomyomatosis, hypersensitivity reactions, bronchocentric granulomatosis, diffuse
pulmonary reticular infiltrates with dysproteinaemia, bronchiolitis obliterans, plasma cell granuloma, effects of exogenous inhalants on the lung, benign clear cell (sugar) tumours, pulmonary veno-occlusive disease, coal-workers pneumoconiosis, eosinophilic pneumonia, pulmonary hypertension, hypertension and vascular disease secondary to polycythaemia, origin of peripheral carcinoid tumours, Wegener’s granulomatosis, desquamative interstitial pneumonia, the relationship of interstitial fibrosis and cancer of the lung, bronchopulmonary sequestration, minute pulmonary tumours resembling chemodectomas, emphysema, air trapping in submarine escape training casualties, right pulmonary isomerism, Marfan’s syndrome, thymic tumours, pulmonary arteriovenous aneurysm, vascular changes with bronchiectasis, vascular changes in chronic pulmonary disease and lung cancer cytology diagnosis. He may not have been the first to describe some of these conditions but it was a legacy that allowed others to build on.

Since Averill Liebow’s passing, there has been recognition of quite a number of diseases including HIV, Helicobacter, hepatitis C, PTLD and SARS. There will be always scope for research and advances undertaken in a manner he championed during his career. It will always be worthwhile to look back at the work of pioneers such him to understand how these diseases have evolved over time and what can we learn from what they found.

Case 1. Spray Painter’s Pneumoconiosis and Basaloid Carcinoma

Dr Andrew Dettrick
The Prince Charles Hospital, Brisbane, QLD

Case History
A 62yo non-smoking man presented with a cough productive of white sputum and slowly worsening SOBOE although he was still working. He had a significant history of interstitial lung disease, ischaemic heart disease (previous CABG) and multiple skin cancers including multiple BCCs one of which was an infiltrative BCC of the left canthus with involved margins requiring re-excision in 2004. High-resolution CT scan showed bilateral widespread increased interstitial opacity with honeycomb changes in a predominantly peripheral distribution, with subtle progression over 6 months. The radiological DDx included UIP and chronic EAA. There was also an incidental 15 x 13mm RUL nodule which showed minor interval increase in size.

He underwent lung wedge for excision of the lung mass and diagnosis of ILD.

Pathology

Tumour:
The tumour was a relatively circumscribed deposit of poorly-differentiated carcinoma located just under the pleura and composed of discrete nests of basaloid cells showing peripheral palisading, abundant mitotic figures and apoptotic bodies and focal squamous differentiation. The tumour was displaying a particular tropism for the basal zone of the airways.

IPX reactions included: p63+; TTF1-; CK34+; CK14+; bcl2+; thrombomodulin+ (squamoid areas +; basaloid areas-); berEP4+; EMA-.

The tumour was arising in an area of fibrosed lung which had been damaged by interstitial lung disease as discussed below.

The previous infiltrative BCC of the canthus with involved margin was retrieved. It looked like a typical BCC and showed basically identical immunoreactivity with the first 6 antibodies listed above.

The lung tumour was considered most likely to represent a basaloid squamous cell carcinoma of the lung arising in the setting of interstitial lung disease in a non-smoker. There is a possibility that it represents a metastasis of basal cell carcinoma from the skin that cannot be entirely excluded.

Interstitial Lung Disease:
Diffuse fibrosing interstitial lung disease was present and showed spatial and temporal heterogeneity. Honeycomb lung was present while there were other areas with no fibrosis (normal lung) and fibroblastic foci were seen. A patchy moderately dense interstitial inflammatory infiltrate dominated by lymphocytes was present which also included occasional eosinophils and plasma cells but no granulomas although there were numerous
interstitial macrophages. Abundant fine black pigment was present together with scattered birefringent crystals. Some bronchioles were involved in the fibrosing process suggesting an element of bronchiolocentricity. The pleura was focally involved. Pulmonary arteries were thickened.

The features best fit into the usual interstitial pneumonia type pattern but were not absolutely typical – there is too much inflammation and the pattern of distribution was not classical. Furthermore, the fibrosis and inflammation were clearly spatially related to the pigment. Taken together, the features were consistent with pneumoconiosis. Although copious black pigment was present, the pattern was not like coal workers pneumoconiosis and there was a lack of appropriate occupational history.

Scanning electron microscopy with energy-dispersive spectrometry was performed by UQ Materials Performance. This identified higher atomic number elements dispersed throughout the tissue. The majority of the particles contended titanium and oxygen, most likely in the form of TiO$_2$. The most common use of TiO$_2$ is as white pigment in paint.

**Diagnosis**
Basaloid squamous cell carcinoma of lung arising in the setting of interstitial lung disease in keeping with spray painters pneumoconiosis.

**DISCUSSION**

**Spray Painters Lung**
Clinically significant lung disease in spray painters is relatively common and symptoms are related to type of painting (spraying), toxic materials (type of paint) used, environmental factors (such as ventilation and use of masks) and length of exposure. Most of the literature surrounding spray painters and lung disease focuses on acute symptoms and illnesses such as asthma, chest pain, cough, sputum production and nose irritation. Chronic lung disease in spray painters has received relatively less attention and includes COPD/Asthma, hypersensitivity pneumonitis, pleural effusions, progressive pulmonary fibrosis and pleural damage. Respiratory function tests generally show a decline in function with a restrictive pattern (Pronk).

Various potentially toxic materials are used in different types of paint: epoxy resins, isocyanates, metal pigments, silica fillers, organic solvents, nanoparticles and polyacrylate (White). Spray painters appear to be at greater risk than other types of painting due to the aerosolisation and therefore higher inhaled dose.

Reports on the histology of spray painters lung are often a bit short on detail. Reports describe various patterns including nodular deposits of brown-black, refractile, polarisable foreign material within alveolar septa, aggregations of macrophages, giant cells, partial emphysema, type 2 pneumocyte hyperplasia, widened alveolar septa and fibrosis (Song, Humble).

Employment as a painter has been listed as a human group 1 carcinogen (IARC 1989). Occupational exposure as a spray painter has been associated with an increased risk of malignancy including urinary tract, testicular cancer and myeloma. The association between painting and lung cancer is more controversial with some studies (Tse) showing a link but not others (Bethwaite). The risk (if real) is probably fairly small after allowing for confounders such as smoking.
Basaloid carcinoma

Basaloid carcinoma (BC) gained traction as a concept during the 1980’s and 1990’s. Brambilla et al introduced the diagnosis to lung pathology in 1992 with a study of 37 cases outlining diagnostic criteria and establishing the poor prognosis of this subgroup of NSCLC. BC was first included in the 1999 WHO classification but was included as a variant of both squamous cell carcinoma and large cell carcinoma – an unfortunate split that caused some diagnostic confusion. In a more recent paper, a study of 90 cases and the largest series to date, Moro-Sibilot et al (including Brambilla) argue for collapsing the 2 variants together.

BC is defined in the 2004 WHO as a proliferation of relatively small cells with a high mitotic rate, having a lobular pattern of growth with peripheral palisading and comedo-type necrosis. The basaloid variant of LCC has no intercellular bridges or individual cell keratinization. Basaloid SCC has obvious squamous differentiation but this must be <50% of the tumour. One can probably add that it must have cytokeratin 34βE12 expression and no neuroendocrine differentiation (<10% of tumour cells showing no more than 1 neuroendocrine marker is acceptable). Unfortunately, the description of the basaloid variant of SCC in the WHO is far too brief to be useful.

BC accounts for around 5-6% of NSCLC. There is a strong male predominance, and mean age is in the 60’s, which are similar to NSCLC’s in general. BC patients have a significantly higher number of pack-years of smoking and are more strongly associated with carcinoma in situ (possibly explained by the extra smoking).

BC is said to have ‘peculiarly aggressive behaviour, characterised by a high frequency of lymph node and visceral metastases’. Some studies have found that BC patients have shorter survival than non-BC NSCLC for all stages (median survival 29 versus 34 months) (Moro-Sibilot). However, other studies have failed to confirm this aggressiveness. Kim et al reviewed 35 cases from Korea and did not find a significant difference in survival between BC and poorly-differentiated SCC. Wang et al found much the same in a series of 22 cases from China.

Treatment at present is chemotherapy and surgery. There are some biomarkers being investigated (such as ERCC1 and P27).

The diagnosis of BC can be a pitfall, especially on small biopsies. The DD includes poorly-differentiated SCC, adenoid cystic carcinoma, small cell or large cell NE carcinoma. Adenoid cystic ca lacks high mitotic count and comedo necrosis. SCLC and LCNE can usually be ruled out with IPXs (CK34-, NE markers+). Poorly-differentiated SCC may be more problematic as it is merely a matter of degree of squamous vs basaloid differentiation that makes the call between the 2. It has been suggested that in practice BC is too frequently assimilated into the SCC category (Moro-Sibilot).

Bibliography

Spray Painters Lung
Pronk et al. Different respiratory phenotypes are associated with isocyanate exposure in spray painters. Eur Respir J. 2009;33:494-501
Humble et al. Titanium particles identified by energy-dispersive X-ray microanalysis within the lungs of a painter at autopsy. Ultrastruct Pathol. 2003;27:127-9

**Basaloid Carcinoma**

Case 2. Molecular Aspects of Mesothelioma: BAP1 and Mesothelioma

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Case: Peritoneal biopsies from a 72-year-old woman (slide included). At laparoscopy, there were multiple peritoneal small nodules, particularly within the right upper quadrant and to a lesser extent in the left pericolic region but the omentum was normal and there was no disease over the mesentery. No pelvic disease was seen. There was a previous hysterectomy (pathology unknown). The laparoscopy was performed as part of work up for potential surgery for liver malignancy (slide also included). A potential primary site was not identified for the liver lesion. There was also a history of uveal melanoma.

Discussion: Many authorities believe that some cases of mesothelioma are associated with a genetic predisposition to mesotheliomagenesis, based in part upon familial clusters of mesotheliomas (even when asbestos-associated).(3) The chromosomal and molecular events associated with MM have been reviewed in detail by Galateau-Sallé et al(4) and Hammar et al(3) - including deletion of chromosome arms (which include losses in 3p21.1 in about 50% of mesothelioma cases), as well as gains, monosomies, loss of heterozygosity (LOH), deletion of p16\textsuperscript{INK4A}, simian virus 40 (SV40), inactivation of the neurofibromatosis 2 (NF2) gene and the fragile histidine triad (FHIT) gene. No consistent or specific chromosomal abnormality in mesothelioma has been identified, though studies on the chromosomal profiles have revealed multiple abnormalities - usually more than 10 clonal abnormalities in any one mesothelioma.(3)

The chromosomal and molecular events associated with MM have been reviewed in detail by Galateau-Sallé et al(4) and Hammar et al(3) - including deletion of chromosome arms (which include losses in 3p21.1 in about 50% of mesothelioma cases), as well as gains, monosomies, loss of heterozygosity (LOH), deletion of p16\textsuperscript{INK4A}, simian virus 40 (SV40), inactivation of the neurofibromatosis 2 (NF2) gene and the fragile histidine triad (FHIT) gene. No consistent or specific chromosomal abnormality in mesothelioma has been identified, though studies on the chromosomal profiles have revealed multiple abnormalities - usually more than 10 clonal abnormalities in any one mesothelioma.(3)

The tumour suppressor gene BAP1 in the 3p21 region has been found to inhibit cell growth, and BAP1 mutations have since been found in a variety of tumours, including breast, renal cell and lung carcinomas and meningiomas, among others (reviewed by Murali et al(5)). Wiesner et al(6) have described germline mutations in two European families with an autosomal-dominant syndrome of multiple melanocytic tumours that included tumours with atypical Spitz-like appearances,(7) and cutaneous and uveal melanomas.(6) These authors(6) found that in all tumours with chromosome 3 loss, it was the paternal copy that was lost, whereas the maternal copy was retained, and the findings suggested that a mutated gene in
the 3p21 region was inherited from the maternal side of the family.(6) Among sporadic tumours with no family history, Wiesner et al(6) found that 40% of uveal melanomas and 5% of cutaneous melanomas harboured somatic BAP1 mutations, and BAP1 mutations have been reported in >80% of metastasising uveal melanomas.(8) In the two families studied by Wiesner et al.(9) four members developed mesothelioma (two pleural, one peritoneal and one pleuro-peritoneal mesothelioma).

Recently, Testa et al(10) reported germline mutations affecting BAP1 in two US families without identifiable asbestos or erionite exposure but with a high incidence of mesothelioma, indicating biallelic inactivation. Of six affected members of one family, four had mesothelioma and the other two had breast or renal cell carcinoma. These authors(10) found that two cases of sporadic mesothelioma had a past history of uveal melanoma, and they found BAP1 mutations in 4/18 (22%) of sporadic mesotheliomas (Bott et al(11) reported a similar rate of about 20%). Bott et al(11) found BAP1 deletions, mutations or both, in 19%, 11% and 11% of mesotheliomas overall. Yoshikawa et al(12) identified BAP1 mutations in 61% of mesotheliomas, significantly more frequent in epithelioid mesotheliomas (81%) than in biphasic or sarcomatoid mesotheliomas 1/3 and 0/4 cases respectively), but Bott et al(11) did not find any association between somatic BAP1 mutations and mesothelioma subtype. Testa et al(10) also found that re-expression of BAP1 in BAP1-deficient cell lines inhibited the colony-forming capacity of those cells: they suggested that individuals with BAP1 mutations have enhanced susceptibility to the mesotheliomagenic effects of asbestos.

In a recent review of BAP1-associated tumours(5), the mesotheliomas in related family members with a germline BAP1 mutation but -'... no history of significant asbestos exposure ...' - comprised bland-appearing epithelioid cells disposed as cords, tubules and papillary formations, with a resemblance to well-differentiated papillary mesothelioma. In those familial cases, one patient died within two years, but the others survived for 2, 6 and 8 years, suggesting a more indolent course in comparison to conventional sporadic MM.(5)

Further investigation of BAP1 mutations in MMs are clearly required, to ascertain: (i) whether such BAP1 mutations correlate with a known histological subtype; (ii) whether they correlate with the presence of WDPM-like papillary formations in sporadic mesotheliomas; and (iii) whether they correlate with more prolonged survival than MMs without them.

**Bibliography**


Case 3. ROS1 rearrangement in lung adenocarcinoma

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- ROS1 rearrangement in lung adenocarcinoma although uncommon, is an important mutation to identify as it is amenable to targeted therapy
  - A recent clinical trial of crizotinib in ROS1-rearranged non-small-cell lung cancers (NSCLCs) revealed marked anti-tumour activity
  - Crizotinib, a tyrosine kinase inhibitor has previously been approved for use in anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC
- The most prevalent mutated oncogenes in NSCLCs are v-ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS), epidermal growth factor receptor (EGFR), ALK, ROS1, ERBB2, BRAF and PIK3CA
- ROS1 gene rearrangement was first identified in human glioblastoma cell lines in 1987 and more recently in lung adenocarcinoma.
- ROS1 is a tyrosine kinase receptor and is normally expressed in the lung as well as other organs, although its exact function is unclear.
- ROS1 fusion leads to constitutive phosphorylation and aberrant activity of the intracellular tyrosine kinase domain which leads to downstream signalling of several oncogenic pathways
- A recent study of 799 resected non-small cell lung cancers by reverse transcriptase polymerase chain reaction (PCR) found 15 tumours harboured the ROS1 fusion transcripts (2.5% of adenocarcinomas), although other studies have found the incidence to be under 2%
  - The most frequent fusion partners were found to be CD74 followed by EZR
  - The patients were often younger non-smoking females
  - Overall survival rates were similar to the ROS1 fusion-negative patients
  - Histologic examination revealed solid growth with signet-ring cells or cribriform architecture with abundant extracellular mucin in 53% of cases (similar to ALK-rearranged tumours)
  - None of the rearranged tumours harboured EGFR, KRAS, HER2, ALK or RET mutations
  - FISH was found to be a reliable diagnostic tool for ROS1 fusion-positive tumours
- Immunohistochemistry with the D4D6 rabbit monoclonal antibody has been reported to detect ROS1 fusions with high sensitivity and no false-positive identifications
- ROS1 can be added to the growing list of gene rearrangements causing non small cell lung carcinoma in never-smokers, along with ALK and EGFR.


Case 4. Acute fibrinous organising pneumonia

Dr Kenneth Lee
Concord Repatriation General Hospital, Sydney Australia.

Acute fibrinous organising pneumonia (AFOP) is a recently described entity by Beasley et al. It possibly represents a fibrinous variant of diffuse alveolar damage (DAD). AFOP is a histologic pattern that can be encountered in patients who present clinically with acute respiratory distress syndrome (ARDS) or in a less severe form, acute lung injury (ALI). Patients who meet the clinical criteria of ARDS often demonstrate features of DAD. Briefly, DAD is generally divided into two phases, the acute/exudative phase and the organising/proliferative phase. Some authors describe the progression to a fibrotic phase where the original lung architecture may be altered by fibrosis. The changes are often diffuse, involving both lungs and are uniform, unless there are repeated insults whereby lesions of different ages may be seen. The exudative phase is characterised by eosinophilic hyaline membranes lining alveolar spaces with mild interstitial inflammation. These features are often diffuse and may be associated with a degree of pulmonary oedema. Vascular thrombi may be present. These changes often peak around four to five days after the initial insult. Thereafter, these changes progress towards the proliferative phase which is characterised by absorption of the hyaline membranes and uniform formation of loose fibroblastic or fibromyxoid plugs in the alveolar spaces. Type 2 pneumocyte hyperplasia, squamous atypia and metaplasia may be encountered.

In contrast, AFOP is characterised by patchy distribution and involvement of the both lungs. The dominant feature of AFOP is organising fibrin balls in the alveolar spaces and the lack of hyaline membrane formation. These changes have a patchy distribution and involve approximately 50% of the airspaces. The alveolar septa adjacent to the fibrin balls may contain a mild inflammatory infiltrate with type 2 pneumocyte hyperplasia but the intervening lungs between the affected areas show minimal changes. Organising fibroblastic tissue may be seen in varying degrees but this is not the dominant feature and some of the organising fibrous plugs may still retain a central fibrinous core. Cases of DAD may have fibrinous balls but that is not the predominant feature and likewise, cases of AFOP may also have occasional foci of hyaline membranes. However, fibrinous change in cases of extensive bronchopneumonia or frank abscess formation should not be diagnosed as AFOP. Clinical presentation of AFOP also differs from DAD. Patients with DAD often require mechanical ventilation. However, only approximately 30% of patients with AFOP changes require mechanical ventilation and the clinical presentation is not always that severe. Unfortunately, despite the apparent less severe clinical presentation and course, the mortality rate is similar to DAD, around 50% and there are no histologic features distinguishing these two groups prognostically. AFOP may be idiopathic but there are also other conditions which may be associated with this pattern of acute lung injury and these conditions are similar to those associated with DAD. These include collagen vascular disease/immune mediated disease, drugs, toxins, occupational exposure, sepsis, shock and infection. Of these, the identification
of an infective source as a causative agent is probably most important when an AFOP pattern is identified.

Histologically, other differential diagnoses of acute lung injury may also share some features with AFOP but there are distinct differences. DAD has already been discussed above with the presence of hyaline membranes lining alveolar spaces being the dominant feature and not organising fibrin balls within alveolar spaces. The patchy distribution of AFOP with unaffected intervening lung is also distinct from the diffuse involvement of DAD. Organising pneumonia (OP) shares a similar pattern in terms of patchy distribution within the lungs but loose fibroblastic tissue is the predominant feature and not organising fibrin balls. In addition, the clinical presentation and outcome differs significantly with AFOP as the mortality rate of OP is less than 10%. The other diagnosis to consider is eosinophilic pneumonia (EP). EP may present either as acute or chronic EP. Chronic EP has a protracted clinical course of a few weeks as opposed to a few days in comparison to acute EP. The salient feature of EP is the presence of large numbers of eosinophils and macrophages. The eosinophils are often in alveolar spaces and may form eosinophilic abscesses. The proportion of eosinophils and macrophages vary and they may also be intermixed with intra-alveolar fibrin. In addition, eosinophils are also present in the interstitium. Although intra-alveolar fibrin deposition in EP is similar to AFOP, but AFOP generally lacks eosinophils or when present, they are inconspicuous. Furthermore, patients with chronic EP tend to have peripheral eosinophilia whilst patients with AFOP have a normal peripheral eosinophil count.

In conclusion, AFOP is a distinct histologic pattern different from DAD, OP and EP. AFOP does share some histologic features with DAD, OP and EP but there are distinct features which allow its separation. It is believed that AFOP may represent a fibrinous variant of DAD. AFOP is a histologic pattern that can be encountered in patients presenting with ARDS or ALI. Although the clinical presentation may not be as severe as compared to DAD, mortality rate is similar to that of DAD. AFOP may be idiopathic but there are several associated conditions which may lead to an AFOP pattern and these conditions are similar to those encountered with DAD. However, the identification of infection is probably the most important in terms of the pathologist’s role in altering or directing clinical treatment for those who present with an AFOP pattern of acute lung injury.

References


Case 5. Chronic Hypersensitivity Pneumonitis --- an Unusual Cause for Lung Transplant

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Case History

A 47 years old lady had a bilateral lung transplant due to end stage lung disease. Six years prior to her lung transplant, a lung wedge biopsy was performed to investigate cause of her SOB and CT findings of bilateral pulmonary infiltrate. The preferred histological diagnosis at the time was hypersensitivity pneumonitis, however clinically the precise allergen was unable to be determined. The patient’s condition progressively deteriorated. Her lung function test showed reduced lung capacity and restrictive pattern of injury. She also has a history of long standing urticaria.

Histopathology

1. Lung wedge biopsy:
The wedge biopsy showed peripheral lung tissue covered by normal pleura. There was a diffuse interstitial chronic inflammatory cell infiltrate with small areas of relatively normal looking lung parenchyma. The inflammation is composed of lymphocytes and plasma cells. This resulted in narrowing of the alveolar spaces which are focally filled with macrophages and occasional giant cells. Scattered multinucleated giant cells were also seen in the alveolar septa. Away from the inflammation, the relatively normal looking lung parenchyma is over inflated.

Necrosis, well formed granulomas, fibrosis, or remodelling of the lung structure were not seen. The preferred histological diagnosis was hypersensitivity pneumonitis.

2. Explanted lung:
Both right and left lung showed similar changes. Macroscopically the lungs appeared firm and solid with focal areas of cystic change. Microscopically the lungs showed patchy consolidation alternating with a few areas of normal looking lung parenchyma. The consolidation is focally due to extensive confluent peribronchiolar fibrosis with remodelling of the lung structure, numerous fibroblastic foci, mild interstitial chronic inflammation, and accumulation of macrophages within the residual alveolar spaces. In other places, the
consolidation was due to interstitial fibrosis resembling sclerosing phase of non-specific interstitial pneumonia (NSIP). In addition, there are numerous multinucleated giant cells which are present either in residual alveolar spaces, alveolar septa, or in the bronchial mucosa. Some airways appeared cystically dilated with chronic inflammation. The pulmonary arteries showed mild intimal fibrosis in keeping with secondary pulmonary hypertension. No well formed granulomas were seen.

Based on the mixed morphology resembling usual interstitial pneumonia (UIP) or NSIP, and the presence of large numbers of multinucleated giant cells, in conjunction with the result of the previous wedge biopsy, the diagnosis of chronic hypersensitivity pneumonitis was established.

**Discussion**

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a diffuse interstitial lung disease, caused by inhalation of various antigens, organic dusts and chemicals. Clinically HP is usually classified into three forms: acute, subacute, and chronic forms.

Chronic HP is thought to develop from very low level persistent or recurrent exposure to an antigen and is separated from other two forms of HP clinically by the presence of fibrosis on radiographic examination. Clinically these patients start with slowly progressive shortness of breath, but frequently develop severe irreversible physiologic impairment. Diagnosis of chronic HP is relying on the combination of clinical features, radiological features and histopathological features of lung biopsy. Within a proportion of patients, definite history of antigen exposure has never been found.

Chronic HP typically manifests on chest radiographs as mid to upper lung zone fibrosis (1). CT findings include small nodules, irregular linear opacities, traction bronchiectasis, architectural distortion, and honeycombing changes.

Histopathologically chronic HP has been reported to show variable morphologies including UIP-like fibrosis, NSIP-like changes, peribronchial fibrosis, and organizing pneumonia like-changes with scattered airway associated multinucleated giant cells (2, 3, 4, and 5). It can be confused with idiopathic interstitial lung disease such as UIP and NSIP. Differentiating between these interstitial lung diseases is dependent on: 1, Sufficient and diagnostic material (lung wedge biopsy) for examined due to patchiness of variable morphological changes; 2, Presence of combined morphological features of UIP-like areas and NSIP-like areas; 3,
Presence of airway associated multinucleated giant cells; and 4, Presence of areas which resemble acute HP and other features such as bronchiolitis, localized organizing pneumonia, lymphocytic alveolitis, and lymphoid follicles; 5, Correlation with clinical and radiological results.

It has been reported that chronic HP is generally associated with a poor prognosis, in particularly those cases which show predominant UIP-like changes (6). Occasionally patients with chronic HP will end with lung transplant due to the end stage lung fibrosis.

Reference


Case 6. Pulmonary MALT Lymphoma with Extensive Amyloid Production

Dr Nicola Kingston

Auckland Hospital, Auckland, New Zealand

Clinical history:
This previously well 51 year old man presented with acute cardiac-type chest pain. He underwent a CT coronary angiogram that showed normal coronary arteries, however a 28mm lobulated, partially calcified, “pleural” mass was identified in the right paravertebral gutter. A PET CT showed the mass was probably in lung parenchyma and had low FDG uptake. A CT guided lung FNA was inconclusive. The patient proceeded to a wedge resection of the lung nodule.

Pathological findings:
The laboratory received a wedge of lung tissue and sectioning revealed a well circumscribed tan, solid subpleural mass, 30mm in maximum dimension. A subcarinal lymph node was also received.

Light microscopy showed the mass was composed of a large nodule of amorphous eosinophilic material containing scattered aggregates of multinucleate giant cells and foci of calcification and ossification. There were also lymphocytes and plasma cells scattered within the mass and aggregated at the periphery. A Congo red stain was positive and showed apple green birefringence under polarised light microscopy, confirming the eosinophilic material to be amyloid.

Immunohistochemistry revealed the vast majority of the lymphocytes were CD20 positive B-cells. Many of the plasma cells stained with lambda and smaller numbers stained with kappa, indicating light chain restriction. Light chain restriction was unable to be demonstrated in the lymphocytes. The amyloid also appeared to stain with lambda. CD5, CD10, CD23 and cyclin D1 were all negative, as was CD43.

FISH was performed on a paraffin block, using the 18q21 MALT1 breakapart probe, and MALT1 gene rearrangement was detected. This may represent either the t(11;18) (q21;q21)
or the t(14;18) (q32;q21) translocation. These translocations are highly specific for MALT lymphoma.

A diagnosis of pulmonary marginal zone lymphoma of mucosa associated lymphoid tissue (MALT), with extensive stromal amyloid deposition was made. The lymph node was not involved by tumour.

Discussion:

Amyloid in the lung can occur in several forms, including diffuse alveolar septal, tracheobronchial and nodular parenchymal amyloid. Diffuse alveolar septal amyloid usually occurs as part of generalised systemic amyloidosis, whereas tracheobronchial and nodular parenchymal amyloid are typically isolated to the lung.\(^1\) Nodular parenchymal amyloid is relatively rare and is usually an incidental finding.\(^2,3\) It may occur as single or multiple nodules.\(^2,3\)

Until recently the cause of pulmonary nodular amyloid deposits was uncertain. Many cases were attributed to chronic inflammatory processes of the lung, such as connective tissue disorders, tuberculosis and HIV infection,\(^4,5,6\) and it was thought that these conditions lead to abnormal production or clearance of immunoglobulins.\(^7\) Nodular amyloidomas have also been attributed to systemic lymphoproliferative disorders, particularly myeloma and lymphoplasmacytic lymphoma. However, it has become increasingly clear that the majority actually represent pulmonary MALT lymphoma with extensive stromal amyloid deposition that obscures the tumour.\(^8\) Although there are still some cases that are not associated with underlying MALT lymphoma, these appear to be much less common.\(^8\)

Regardless of whether or not the nodular amyloid is related to underlying lymphoma, the histologic features are similar. The lesions are composed of a large mass of amorphous eosinophilic material, that is positive with Congo Red staining and shows apple green birefringence under polarised light. The amyloid may be associated with giant cells and sometimes shows calcification and ossification. A mild infiltrate of lymphocytes and plasma cells is seen both within and surrounding the amyloid.

In cases of MALT lymphoma with extensive amyloid production, the features of the surrounding lymphocytes and plasma cells are similar to those seen in typical MALT lymphoma, although they often have a more prominent plasma cell component.\(^9\) However, the diagnosis can easily be overlooked as the amyloid can obscure the underlying tumour.
Therefore it is imperative to investigate these lesions thoroughly, even if only scanty lymphocytes are present.

Several morphologic features have been reported that should alert the pathologist to the possibility of lymphoma, and these include lymphatic tracking, sheet-like clusters of plasma cells, pleural infiltration and the presence of reactive lymphoid follicles.\textsuperscript{10} Immunohistochemistry is important, with CD20 positivity in the majority of lymphocytes being perhaps the most helpful clue in highlighting the presence of lymphoma. Demonstrating light chain restriction in either the lymphocytes or plasma cells is also important. MALT lymphomas may show CD20/CD43 coexpression, and are typically negative for CD5, CD10, CD23 and cyclin D1.\textsuperscript{9,10}

Occasional cases of MALT lymphoma from a variety of sites are associated with stromal amyloid production.\textsuperscript{11} Although this is more common in the lung than other sites, it is still relatively rare (1\%\textsuperscript{10}– 6\%\textsuperscript{12}). Proportions of amyloid within the tumours vary, but in one study the amyloid comprised greater than 90\% of the lesion in 35\% of cases.\textsuperscript{11} A recent study showed that the amyloid in these lesions is derived not only from immunoglobulin light chains, but also heavy chains, both produced locally by the neoplastic plasma cells.\textsuperscript{8}

MALT lymphomas with amyloid production have an indolent behaviour similar to that of MALT lymphoma without amyloid. Amyloid production does not confer a worse prognosis.\textsuperscript{11} Furthermore, local amyloid deposition within a MALT lymphoma is not typically associated with systemic amyloidosis and therefore extensive investigations for systemic amyloid are not required.\textsuperscript{11}

In summary, the majority of lesions traditionally diagnosed as nodular pulmonary amyloidoma are in fact MALT lymphomas with extensive amyloid production obscuring the underlying tumour. Therefore, the finding of nodular amyloid deposition in the lung should prompt a thorough search for lymphoma.

References:


