COMPANION MEETING

LUNG

Bayside Room 102
Time: 11:15 – 1:00

Convenor: Dr Jenny Ma Wyatt, PathWest, QEII, Perth, WA

Lecture 1  Associate Professor Wendy Cooper, Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, NSW. Non-small cell lung cancer. What's new for pathologists.

Lecture 2  Dr Prudence Russell, St Vincent’s Pathology, Melbourne, VIC. Does lung adenocarcinoma subtype predict patient survival?

Lecture 3  Prof Stephen Fox, Peter MacCallum Cancer Centre, Melbourne, VIC. EGFR mutation testing in lung carcinoma.

Case Presentations:
Case 1  Dr Tina Baillie, Douglass Hanly Moir Pathology, Sydney, NSW. A case of Churg-Strauss Syndrome

Case 2  Dr David Godbolt, Northside Pathology/Pathology Queensland, QLD. Pulmonary extramedullary haematopoiesis in the context of myelofibrosis

Case 3  Dr Annabelle Mahar, Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, NSW. An unusual cytokeratin positive spindle cell tumour

Case 4  Dr Lisa Lin, ICPMR, Westmead Hospital, Sydney, NSW. Spindle cell variant of juvenile xanthogranuloma
CASE HISTORIES

Convenor: Dr Jenny Ma Wyatt, PathWest QEII, Perth, WA

Case 1. Dr Tina Baillie, Douglass Hanly Moir Pathology, Sydney, NSW

A 42 year old Japanese male, recently arrived in Sydney, presented on 6 September 2010 with neck pain and stiffness, lumbar pain and aching calf muscles, paraesthesia of the left hand and foot and cervical lymphadenopathy. He had a background history of adult onset asthma with "eosinophilic lungs" (?pulmonary interstitial eosinophilia) and was on multiple asthma meds. Recent blood test showed a "remarkable rise in eosinophils" and raised liver function tests.

Case 2. Dr David Godbolt, Northside Pathology/Pathology Queensland

72 year old woman with diffuse mosaic ground glass opacities on CT who had previously been treated with hydroxyurea for ?MDS.

Case 3. Dr Annabelle Mahar, Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, NSW.

Mass at hilum of right lung. No pre-operative tissue diagnosis. Bilobectomy performed (middle and lower lobes).

Case 4. Dr Lisa Lin, ICPMR, Westmead Hospital, Sydney, NSW

A 23 year old female underwent a left lung lower lobectomy for a 2.5cm lesion detected incidentally on a chest x-ray performed for epigastric pain.
NON-SMALL CELL LUNG CANCER. WHAT’S NEW FOR PATHOLOGISTS.

Pathologists face new challenges in the diagnosis and classification of non-small cell cancer (NSCLC). Unlike in the past, accurate distinction of adenocarcinoma from squamous cell carcinoma (SCC) is now clinically important due to impacts on therapeutic choices and determining suitability for molecular testing. A new International Multidisciplinary Classification of Lung Adenocarcinoma has recently been published under sponsorship of the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. This classification addresses a number of clinically relevant issues regarding adenocarcinomas including uniform terminology and diagnostic criteria and an approach to small biopsy specimens. New diagnostic terms have been introduced for resection specimens including adenocarcinoma in situ (AIS; virtually all are non-mucinous) and minimally invasive adenocarcinoma (MIA) while the term bronchioloalveolar carcinoma is no longer used. For invasive adenocarcinomas, the predominant pattern is required for classification (lepidic, acinar, papillary, micropapillary or solid) and sensibly, the term “mixed subtype” is no longer used since the vast majority of tumours fell into this category. Using this approach, potentially useful information regarding associations between histological patterns of adenocarcinoma and tumour behaviour or molecular features may be more clearly elucidated.

A number of recent clinical trials have highlighted clinical relevance of differentiating adenocarcinoma from SCC.

(i) Patients with non-squamous histological subtypes of NSCLC have superior response rates and survival following treatment with the chemotherapeutic agent pemetrexed, an antifolate anti-metabolite which targets thymidylate synthetase. The molecular basis underlying the differential efficacy probably relates to lower levels of thymidylate synthetase in adenocarcinomas compared to squamous cell carcinomas. Histological subtypes of NSCLC have not previously shown any consistent differential sensitivity to chemotherapeutic treatments but these recent studies confirm a predictive role of NSCLC histological subtypes in determining efficacy of pemetrexed.

(ii) Patients with SCC subtype of NSCLC may develop life-threatening pulmonary haemorrhage following treatment with the anti-vascular endothelial growth factor antibody bevacizumab and should not receive this treatment.

(iii) Almost all NSCLCs harbouring epidermal growth factor receptor (EGFR) mutations are adenocarcinomas and tumours with these mutations are more responsive to EGFR tyrosine kinase inhibitors (TKI) than wild type tumours. EGFR mutant lung cancers are more commonly found in patients who are non-smokers, female and of Asian ethnicity. Accurate histological subtyping of NSCLC subtypes is important in helping to select which cases are appropriate to undergo mutation testing. Implementation of EGFR mutation testing requires a multidisciplinary...
approach and should be considered in patients with adenocarcinoma, cases of lung cancer with unclear histological subtype and NSCLC patients who are “never smokers”, regardless of tumour histology. There may be discrepancy between EGFR status in primary and metastatic tumours, but until this is better understood, biopsy material from the most easily accessible site is suitable for mutation testing.  

(iv) A small proportion of NSCLCs harbour rearrangements of the ALK gene (anaplastic lymphoma kinase) and these tumours are of interest due to the development of targeted ALK inhibitors. NSCLCs with ALK rearrangements are almost all adenocarcinomas and tend to be found in patients with similar clinicopathological features to those with EGFR mutations. These tumours are sensitive to ALK kinase inhibitors in vitro and in vivo and clinical trials are currently being undertaken with these agents.

While there is evidence for the importance of distinguishing histological subtypes of NSCLC, studies of interobserver variability have generally shown only moderate agreement between pathologists in the distinction of lung adenocarcinoma from SCC. In addition, as 65 – 75% of patients with NSCLC present with advanced stage disease, the diagnosis is usually based on small biopsy or cytology samples alone, producing greater challenges for accurate subtyping. In small biopsy samples, one study found only 63% of NSCLC could be correctly subclassified in bronchial biopsies and 45% in cytology samples. Others have shown only about 50% of small biopsies enable subtyping of NSCLC.

Light microscopic evaluation of morphology enables subclassification NSCLC in most cases, however, ancillary tests can be of assistance in further classifying cases of “non-small cell lung carcinoma, NOS”. Two recent studies suggest the most useful panel consists of TTF-1 and a mucin stain for identification of adenocarcinomas, and p63 and CK5/6 for SCC. However, no single marker or panel of markers is completely sensitive or specific for subclassification of NSCLC and results should always be interpreted in the context of morphological and clinical features. Furthermore, additional stains should be used judiciously in order to preserve tissue for molecular testing.

References


DOES LUNG ADENOCARCINOMA SUBTYPE PREDICT PATIENT SURVIVAL?

A new adenocarcinoma classification called the International Association for the Study of Lung Cancer (IASLC) / American Thoracic Society (ATS) / European Respiratory Society (ERS) International Multidisciplinary Lung Adenocarcinoma Classification was developed by an international multidisciplinary panel of lung cancer experts, first presented in 20091 and published in 2011.2 The rationale behind the development of the new classification was the many advances in the practice and understanding of oncology, surgery, radiology and molecular biology of lung adenocarcinoma since the publication of the 2004 World Health Organisation Classification of Lung Tumors.3 In addition, it had been shown that classification of lung adenocarcinomas according to the 2004 WHO classification resulted in most tumours being allocated to the adenocarcinoma of mixed subtype category4 and that a disconnect still existed between the strict pathologic definition of bronchioloalveolar carcinoma5 (BAC) and the clinical use of the term.6-10 Some of the main aims of the new classification include incorporation of significant practice changing advances in the fields of pathology, molecular biology, oncology, radiology and surgery into a classification that is still principally based on histopathologic examination and to provide consistent terms and diagnostic criteria for adenocarcinoma subtypes, particularly for BAC and mixed subtype adenocarcinoma.

Some important changes in the new classification include:

1. Making the term BAC obsolete.
2. Renaming BAC, adenocarcinoma in situ (AIS) and defining it as a small (<3cm) solitary lesion with 100% lepidic growth.
3. Introducing minimally invasive adenocarcinoma (MIA), an entity previously sometimes referred to as minimally invasive BAC7 that was not included in 1999/2004 WHO classifications, and defining it as a small (<3cm) solitary adenocarcinoma with predominant lepidic growth and ≤5mm invasion.

If resected both AIS and MIA are associated with 100% or near 100% disease-free survival5,11,12 AIS and MIA are usually non-mucinous, though rare examples are mucinous and called mucinous AIS and mucinous MIA in the new classification.

4. Making the term adenocarcinoma of mixed subtypes obsolete.
5. Dividing mixed subtype adenocarcinoma into five invasive subtypes on the basis of comprehensive histologic subtyping.4

Comprehensive histologic subtyping is a recently introduced process in which each histopathologic subtype present in a tumour is estimated in 5% increments followed by identification and classification of that tumour according to the predominant histologic subtype.

6. The five invasive subtypes include three present in previous WHO classifications, acinar, papillary and solid with mucin.
7. Introducing two new subtypes, lepidic and micropapillary patterns:
   a. Lepidic predominant adenocarcinoma (LPA) has predominant lepidic growth with >5mm of invasion and may show tumour necrosis or invasion of lymphovascular spaces or visceral pleura.
b. Micropapillary adenocarcinoma was not included in previous WHO classifications although it was referred to in the 2004 WHO classification and is a pattern of great significance due to its poor prognosis.

8. Variant adenocarcinomas listed in the new classification include invasive mucinous, colloid, enteric and foetal adenocarcinomas.

a. Mucinous BAC has been renamed invasive mucinous adenocarcinoma in recognition that these tumours have components of lepidic growth with columnar or goblet cells with abundant intracellular mucin admixed with invasive adenocarcinoma patterns with stromal invasion. In addition, invasive mucinous adenocarcinoma, when compared to AIS, has different radiologic, immunohistochemical and molecular features as well as prognosis.

b. Mucinous cystadenocarcinoma has been included with colloid carcinoma.

c. Enteric adenocarcinomas have intestinal morphology as well as partial expression of intestinal differentiation.

9. Clear cell variant adenocarcinomas, present in the 2004 WHO classification, have been re-defined as cell types rather and placed for analysis in the subtype/variant in which the cell change occurs. Recently Yoshizawa et al validated the new adenocarcinoma classification with a North American data set comprising 514 stage I lung adenocarcinomas. They demonstrated a correlation between adenocarcinoma subtypes according to the new definitions and survival, indicating a valuable prognostic role for the new classification.

Against this backdrop, we identified 210 patients with surgically resected stages I, II and III lung adenocarcinoma operated on with curative intent between 1996-2009. Two pathologists, blinded to patient outcome, first classified the cases according to the 2004 WHO classification. Then each pathologist independently performed comprehensive histologic subtyping according to the new IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. Kaplan-Meier curves were used to calculate five-year survival for each separate histopathologic subtype/variant. Univariate and multivariate analyses were undertaken to control for validated prognostic factors. We confirmed that the new subtypes of adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic predominant adenocarcinoma had a 5-year survival approaching 100%, whereas micropapillary predominant and solid with mucin predominant adenocarcinomas were associated with particularly poor survival. Papillary predominant and acinar predominant adenocarcinomas had an intermediate prognosis. This effect persisted after controlling for stage.

Classification of lung adenocarcinoma according to the new IASLC/ATS/ERS classification correlated with five-year survival in an Australian cohort of 210 patients with stages I, II and III lung adenocarcinoma. These relationships persisted after controlling for known prognostic patient and tumour characteristics. The new classification has advantages not only for individual patient care, but also for better selection and stratification for clinical trials and molecular studies.
References:
17. Goldstein NS, Thomas M. Mucinous and nonmucinous bronchioloalveolar adenocarcinomas have distinct staining patterns with thyroid transcription factor and cytokeratin 20 antibodies. Am J Clin Path 2001;116:319-325
EGFR MUTATION TESTING IN LUNG CARCINOMA

Until recently lung cancers have been broadly subtyped into small cell and non-small-cell lung cancer (NSCLC). These “clinical” entities mirrored the narrow therapeutic options available to patients. However, a number of driver molecular mutations that occur mostly frequently in adenocarcinomas in females of Asian origin without a strong history of smoking, has lead to a paradigm shift in classification and management of lung tumours. Thus it has become essential to phenotypically characterise lung carcinomas so that testing for mutations in genes such as those in epidermal growth factor receptor (EGFR) can be performed so that patients can be stratified for treatment with anti-EGFR tyrosine kinase inhibitors, gefitinib and erlotinib. Thus these agents have shown to abrogate tumour growth in animal models and increase progression free and overall survival in patients with lung carcinomas harbouring such mutations in the first line setting. EGFR mutations are common in adenocarcinomas but are rarely present in small cell carcinoma, squamous carcinoma and large cell carcinoma. There are morphological clues in tumours harbouring an EGFR mutation including bronchoalveolar features, absence of solid growth pattern, mild lymphocytic host response and absence of mucinous differentiation.

The epidermal growth factor receptor is one of a family of tyrosine kinase receptors expressed by a number of tumour types that on ligand engagement leads to downstream signalling resulting in cell proliferation, cell survival and angiogenesis. Activation of EGFR can also occur when the gene is mutated, as occurs in lung adenocarcinomas. Mutations in EGFR are largely restricted to exons 18-21 and can be classified 4 groups:

Classical activating mutations that exhibit sensitivity to gefitinib and erlotinib which include: exon 19 deletions, Leu858Arg and Leu861X in exon 21 and mutations at codon 719 in exon 18 (Gly719Ala/Ser).
Activating mutations of uncertain gefitinib and erlotinib sensitivity such as exon 20 insertions and duplications.
Resistance mutations such as the common Thr790Met mutation associated with both acquired and primary resistance.
Mutations of unknown significance in terms of activity or drug sensitivity.

After treatment with anti-EGFR inhibitors resistance mutations that were undetectable in previous biopsies can be identified. This may be due to emergence and selective advantage that new DNA alterations give the tumour under treatment or that their presence was at too low a level for their identification. The latter notion is supported by the use of highly sensitive methods that can detect low-level mutations in tissues.

Currently there are no defined standards for EGFR testing. DNA is extracted from formalin fixed paraffin embedded tissues with most testing centres use sequencing.
Adequate tissue is required for such testing but results can be obtained from cytological cell blocks and small biopsies provided the proportion of tumour cells exceed 20% so that mutant allele can be detected above normal EGFR. Mutant specific antibodies have been developed that may reduce costs of molecular testing and enable the identification of mutant EGFR in small biopsies.

EGFR is one of several targetable mutations in lung adenocarcinomas others being ALK kinase rearrangements, HER2 amplification and BRAF. Tests for these changes should also be considered should EGFR gene be wild type.

References:


CASE NO 1.

A CASE OF CHURG-STRAUSS SYNDROME

Dr Tina Baillie, Douglass Hanly Moir Pathology, Sydney

Clinical History: A 42 year old Japanese male arrived in Sydney in March 2010 and presented 6 months later with neck pain, cervical lymphadenopathy and paraesthesia of the left hand and foot. He had a background history of adult onset asthma and was on multiple medications. Prior lung biopsy in Japan in 2002 was reported as eosinophilic lungs (?Pulmonary interstitial eosinophilia). His recent blood tests showed marked increase in eosinophils, with abnormal liver function tests. CXR showed hyperinflation, chronic inflammatory changes in both bases laterally and possible early pulmonary fibrosis. On examination the patient had a palmar rash, and features of mononeuritis multiplex.

A skin punch biopsy was performed which showed acute necrotizing vasculitis with eosinophilic infiltrate.

The patient then underwent liver biopsy, which showed non-specific eosinophilic hepatitis with hepatocyte necrosis and regeneration but no sign of vasculitis (thought to possibly be drug-related).

Lung wedge biopsy was performed which showed pulmonary vasculitis, with eosinophilic infiltration and background changes related to asthma.

A diagnosis of Churg-Strauss syndrome was made.

Churg-Strauss syndrome was originally described in 1951 as an allergic angiitis and granulomatosis. It is a rare systemic disease with clinical and pathologic features that overlap with those of polyarteritis nodosa and Wegener’s granulomatosis. Allergic rhinitis, nasal polyps, and sinusitis are common accompanying features. The exact etiology is unknown, however, abnormal immune function and genetic factors have been identified. Churg-Strauss syndrome (CSS) as originally described is a syndrome characterized by asthma, blood and tissue eosinophilia and in its full-blown form, eosinophilic vasculitis, along with necrotizing granulomas centered around necrotic eosinophils. However, it has become apparent that many cases pass through a series of phases before the development of vasculitis and that some relatively early cases may not demonstrate vasculitis. In many cases CSS responds well to steroid therapy. However, steroids are also used widely in the treatment of asthma itself. In some patients CSS may develop and be accidentally suppressed by the use of steroid therapy.

The differential diagnosis of CSS includes two separate categories: diseases characterized by tissue (largely pulmonary) eosinophilia and other forms of ANCA-positive small-vessel vasculitis.

References

CASE NO. 2

PULMONARY EXTRAMEDULLARY HAEMATOPOIESIS IN THE CONTEXT OF MYELOFIBROSIS

Presented by: Dr David Godbolt, Northside Pathology/Pathology Queensland

While the history submitted at the time of biopsy was of a 72 y.o. woman with diffuse mosaic ground glass opacities on CT who had previously been treated with hydroxyurea for “MDS”, subsequently it was found that the woman had a long history of myeloproliferative disease. A bone marrow biopsy in July 2010 found myelofibrosis. She had no leukaemic infiltrate. Hydroxyurea had been stopped because of the progressive lung interstitial infiltrate.

The biopsy demonstrates a heterogeneous interstitial infiltrate of myeloid and erythroid precursors together with megakaryocytes in keeping with extramedullary haematopoiesis. Patchy organising pneumonia is present in some air spaces.

While lymphoid neoplasms are relatively common in the lung, myeloid disorders are unusual. Other causes of lung disease including infection, haemorrhage, heart failure, the effects of chemotherapy or radiotherapy, alveolar proteinosis and opportunistic neoplasms are more common in a patient with a history of a myeloid disorder and should first be excluded.

Leukaemias complicating the lung are more commonly seen at autopsy rather than in biopsies or resections undertaken during life. While B-CLL is the most common leukaemia involving the lung, any subtype may be seen. Acute myeloid leukaemias more commonly involve the lung than acute lymphoblastic leukaemias1.

This is an example of extramedullary haematopoiesis (EMH) in the context of myelofibrosis (agnogenic myeloid metaplasia). Myelofibrosis is not the only cause of this in the lung and has been reported in thalassemia, erythroblastosis fetalis and hereditary spherocytosis2,3. EMH most commonly involves the reticuloendothelial system – the spleen, liver and lymph nodes. In the context of myelofibrosis, it usually presents in the 6th to 7th decades and 95% of patients have splenomegaly. Clinical course is characterised by slow progression that may be complicated by bleeding, infections, cardiovascular illnesses or leukaemic transformation. Pulmonary EMH has been reported to be complicated by pulmonary hypertension. The aetiology of this is uncertain but megakaryocytes have been implicated1. Treatment options without BMT are generally limited and prognosis is poor2. However, pulmonary EMH usually rapidly regresses after allogeneic haematopoietic stem cell transplantation4.

1. Morice WG, Colby TV. Lymphoproliferative disorders. In Dail and Hammar’s Pulmonary Pathology. 2008
AN UNUSUAL CYTOKERATIN POSITIVE TUMOUR IN LYMPH NODE

By far and away the most common cause of a cytokeratin-positive spindle cell tumour in lymph node tissue is metastatic (“sarcomatoid”) carcinoma. While the site of origin of a sarcomatoid carcinoma might not be apparent from the morphology or immunophenotype of the metastasis, a primary site can usually be established from the clinical history (previous or concurrent), histological examination of associated specimens (e.g., lung, kidney, bladder, skin), or radiological correlation.

Less common causes of cytokeratin-positive spindle cell tumour in excised thoracic lymph node tissue include metastatic sarcomatoid mesothelioma, thymoma, and metastatic sarcoma (e.g. epithelioid sarcoma, epithelioid angiosarcoma and epithelioid leiomyosarcoma). Aberrant cytokeratin expression in non-epithelial tumours such as melanoma, gastrointestinal stromal tumour, and sarcoma accounts for small numbers of cytokeratin-positive intranodal spindle cell tumours. Clinicopathological and radiological correlation and additional immunohistochemistry can be helpful in arriving at the correct diagnosis in such cases.

A population of reticulum cells in normal lymph nodes show positive staining for cytokeratins (usually pancytokeratin and Cam5.2), and appear to be increased in number in some enlarged and pathological lymph nodes. (1-3) These cells have been designated “cytokeratin-positive interstitial reticulum cells (CIRCs)” and it is suggested that they are a form of fibroblastic reticulum cell. The location, immunophenotype and ultrastructural features differ to those of follicular dendritic cells and interdigitating reticulum cells.

Rare cases of intranodal tumours postulated to have arisen from cytokeratin-positive reticulum cells have been described (Gould et al, 1990, 3 cases; Chan et al, 2000, 3 cases). (4, 5) The tumours were reported to show a dendritic morphology, were admixed with reactive lymphocytes, and occurred in the absence of an obvious primary carcinoma at the time of resection or on follow-up of up to 12 years. While the possibility of an occult or regressed primary carcinoma was considered, the authors postulated that the tumours arose from cytokeratin-positive reticulum cells. The term “cytokeratin-positive interstitial reticulum cell tumour” has been suggested. Five of the six cases of cytokeratin-positive reticulum cell tumours occurred in the thorax, three of which were located in lymph nodes at the pulmonary hilum.

In the current (2008) WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, cytokeratin-positive reticulum cell tumours are classified with, or considered to be a subtype of, fibroblastic reticulum cell sarcoma. (6) Although the dendritic and reticulum cell tumours are classified with tumours of haematopoietic origin, the behavior is more in keeping with a soft tissue-type tumour such as a low grade sarcoma.
In view of the extreme rarity of cytokeratin-positive reticulum cell tumours it is important to exclude other causes of cytokeratin-positive spindle cell tumour and, in particular, metastatic carcinoma should be considered in the first instance.

WHO classification of Histiocytic and Dendritic Cell Neoplasms (Chapter 14; 2008)

Histiocytic sarcoma
Tumours derived from Langerhans’ cells
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Other rare dendritic cell tumours

**Fibroblastic reticular cell tumour**
*(including cytokeratin-positive reticulum cell tumour)*

Indeterminate dendritic cell tumour
Dendritic cell sarcoma, not otherwise specified
Disseminated juvenile xanthogranuloma

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REFERENCES:


CASE NO. 4

Presented by: Dr Lisa Lin, ICPMR, Westmead Hospital, Sydney, NSW

THE CASE OF AN UNUSUAL SPINDLE CELL LESION

Case History: A 23 year old female underwent a left lung lower lobectomy for a 2.5cm lesion detected incidentally on a chest x-ray performed for epigastric pain.

Histological Features: Well-circumscribed lesion comprised of intersecting fascicles of spindle cells with hyperchromatic nuclei, minimal nuclear atypia and eosinophilic cytoplasm. Focally, these merged with cells displaying foamy cytoplasm. There were scattered small lymphocytes, mitoses and occasional osteoclast-like giant cells.

IPx: LCA, CD68, CD163, CD4, Factor XIIIa, Vimentin strongly positive. EMA patchy positive. AE1/AE3, S100, SMA, CD99, CD21, CD23, CD35 negative. CD34 highlighted blood vessels only.

Diagnosis: Spindle cell variant of juvenile xanthogranuloma.

Juvenile xanthogranuloma is a non-Langerhans cell histiocytosis seen most commonly in childhood and adolescence. It typically presents as a cutaneous tumour with rapid growth and spontaneous regression within months or years. Juvenile xanthogranuloma of extracutaneous sites are rare, and pose a diagnostic dilemma if there is no prior history of cutaneous component. Only a handful of case reports are present in the literature describing solitary extracutaneous juvenile xanthogranuloma.1-3 We report an interesting and extremely rare case of juvenile xanthogranuloma in the lung without other current or previously excised cutaneous or extracutaneous lesions in a young adult.

Juvenile xanthogranuloma (JXG) is a well-recognised member of the non-Langerhans’ cell group of histiocytic proliferative disorders, with dermal dendocytes considered to be the principal cell type in this entity.4 The first case was described as “congenital xanthoma multiplex” by Adamson in 1905,5 and the term “juvenile xanthogranuloma” was named by Helwig and Hackney in 1954.6 It is a disease primarily found in infants, children and adolescents, and is associated with a variety of medical conditions including neurofibromatosis, Niemann-Pick disease, urticaria pigmentosa and juvenile myelomonocytic leukemia (JMML).7,8 Pathogenesis is largely unknown, however the disease is believed to be a reactive response to an unknown stimuli.9,10

Characteristically, it presents as a solitary or multiple red-brown cutaneous papulonodules on the head and neck, upper part of the trunk and proximal aspects of the limbs. Two-thirds of all cases develop within the first six to nine months of life, and spontaneous involution is usually observed within months or years.11

Extracutaneous manifestations of JXG occur in approximately 5% of cases,10 including involvement of mucosal surfaces, central nervous system, eye, liver, spleen, lung, lymph node and bone marrow.1,2,7 Although these extracutaneous lesions are of benign nature, significant problems may arise due to pressure effects and possible clinical misdiagnosis as malignant entities.
The first adult onset JXG case was reported in 1963. Approximately 15% of JXG occur in adults, with the majority of the cases presenting as solitary cutaneous lesions in the head and neck. They usually occur in the second to third decades, however patients in their 60s and 70s have been known to be affected. Only a handful of adult onset extracutaneous cases have been reported in the literature, involving the eyes, skeletal muscle, breast and gingiva, with most of these cases showing concomitant cutaneous lesions.

Both juvenile and adult forms of disease show a similar spectrum of histological features, displaying a mixture of different mononuclear and multinucleated cell types as described in Zelger et al.’s overview of non-Langerhans cell histiocytoses. Spindle cell variant, characterised by spindle-shaped histiocytes arranged in a storiform pattern, is seen more commonly in adult JXG in favour of vacuolated, xanthomatised, scalloped and oncocytic types, and characteristic Touton cells may be sparse or absent in extracutaneous sites. Regardless, it is believed that the histological variation of JXG lesions is a time-dependent phenomenon rather than age or site dependent, and mirrors the life cycle of the lesion with eventual capacity for self-healing or spontaneous regression. Fortunately for diagnostic purposes, JXG cells show a consistent immunoreactivity for vimentin, CD68, Factor XIIIa and CD163, and are negative for S100, CD1a and Langerin. Electron microscopy show bland fibrohistiocytic and/or xanthoma cells without Birbeck granules. Nonspecific intracytoplasmic findings such as dense bodies, wormlike bodies, and popcorn bodies may be found.

All cases of pulmonary JXG in the literature have been recorded in children to date. All but one of these cases show coexisting cutaneous or other visceral lesions, assisting in the diagnosis of pulmonary JXG. This made our case challenging, given the rarity of pulmonary JXG and the lack of other JXG lesions in our patient.

In summary, juvenile xanthogranuloma should be considered in the differential diagnosis of spindle cell lesion encountered in any organ system and performing the appropriate immunoperoxidase panel to exclude other conditions is the key to diagnosis.

References