Path, QLD - Sunshine Coast University Hosp
at Doherty Street
Nambour 4560
ph: [redacted]
fax

Patient Location	Mortuary (SCUH)	**UR No**	ORR292964 **Sex** M
Consultant	Dettrick, A	**Name**	HANSEN
This report to:	**Dr Michael Sean McManus**	**Given Name**	Peter
	Mackay Hospital	**DOB**	06-Oct-1950
	475 Bridge Road	**Patient Address**	[redacted]
	Mackay QLD 4740		

Collected: 21:30 06-Oct-21 **Lab No** 20529-13033 **PM No**

Autopsy Report

Autopsy No:

SC21A41 HANSEN Peter ORR292964

Date of Admission: 04/10/2021

Date and time of Death: 06/10/2021 at 2130

Date and time of Autopsy: 19/10/2021 at 0800

Pathology Registrar: Dr Alyona Dziouba

Supervising Pathologist: Dr Andrew Dettrick

Mortuary technician: Krissy Wallace
(Medical students in attendance)

HISTORY

Peter HANSEN (URN MKH 235572) is a 70 year old male born on the 06/10/1950.

The patient was referred from Proserpine Hospital to Mackay Base Hospital (MKH) for severe community acquired pneumonia with possible underlying interstitial lung disease and type 1 respiratory failure. He had been unwell for 3 weeks with progressive shortness of breath. His partner reported reduction in exercise tolerance over the years. The patient had been initially treated with ceftriaxone and doxycycline at Proserpine Hospital however continued to deteriorate with increased oxygen requirements. Following admission to MKH, a CT pulmonary angiogram was performed (4/10/2021) to exclude a pulmonary embolus (PE) which showed no evidence of a PE however showed cystic lung disease, with thin walls and an upper zone predominance. Multiple paratracheal, mediastinal and hilar lymph nodes were also noted with the largest measuring 20mm (reactive vs. neoplastic vs. granulomatous). The patient continued to deteriorate on admission, and a decision was made to proceed to intubation and ventilation on the 4/10/2021. The patient was subsequently reviewed by the respiratory team, who felt that the patient would be unlikely to respond to steroids given the degree of fibrosis on imaging and following discussion with the family, a palliative route of care was initiated. The patient died on the 6/10/2021. The patient's family have requested that his body be submitted for autopsy.

Past Medical History:
- Hypertension
- Type 2 diabetes mellitus
- COPD
- E-cigarette user; Ex-traditional smoker - quit 10 years ago, 40 pack year

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history
- Ex-heavy alcohol use

Salient antemortem pathology results:
Hb 145, WCC 19.7, neuts 16.86
Blood cultures x 4:
- Positive for S. epidermis (1 of 2 bottles at 40 hrs) (likely contaminant)
- Positive for S. capitis (1 of 2 bottles at 89.7 hrs) (likely contaminant)
- 2 x negative at Proserpine

CRP 172
M. pneumoniae Ab 80, L. pneumophila 1 and 2 < 64
Urine MCS, L. pneumophila and S. pneumonia antigen negative
COVID and respiratory PCR viral panel negative

Medical Certificate Cause of Death:
1a: Severe interstitial lung disease (months to years)
2: Smoking (years)

Consent is granted for a full autopsy.

EXTERNAL EXAMINATION
Identifying features:
There is a hospital identification tag on the left wrist.

Physical characteristics:
Height 176cm, Weight 96kgs. (BMI 31)

The body is that of an adult Caucasian male showing an appearance consistent with the stated age. The build is large. The hair is short and brown/grey in the usual male pattern. The external ears and nose are unremarkable. The lips and mouth are unremarkable.

External examination reveals a white area of possible scar at the left upper thigh. There is a dry, patchy rash over the left anterior shin. There is mild central oedema. There are no congenital or acquired deformities.

Signs of Post mortem change:
There is post mortem hypostasis distributed over the posterior surface of the body. Rigor mortis is absent. There is no evidence of decomposition.

Signs of recent therapy:
There are some signs of venepuncture over the right and left arm near the antecubital fossae. There are signs of attempted vascular access at the right anterior neck and left wrist. There is a dressing over the sacral area, however no skin changes are present underneath the dressing.

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Pathology Queensland (NATA/RCPA Corporate Accreditation Number 2539)
Health Support Queensland

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Signs of recent injury:
There are no signs of recent injury.

INTERNAL EXAMINATION

Cardiovascular System
The heart is slightly large and floppy; it weighs 450g (expected = up to 430g by body weight). The pericardium is normal and there is a small clear serous pericardial effusion. The heart comprises 4 chambers in the usual sequence and is normally sited. No thrombi or emboli are noted anywhere within the cardiovascular system.

The right atrium is not dilated and receives the superior and inferior caval veins. The right atrial appendage is normal and does not contain any thrombus. The oval fossa is normal and no interatrial septal defects are noted. The tricuspid valve is normal, composed of 3 leaflets and has a circumference of 135 mm. The tricuspid valve drains to the right ventricle. The right ventricle is not dilated, the right ventricular free wall measures 5 mm in thickness and the right ventricular outflow tract is muscular. The pulmonary valve comprises 3 leaflets and has a circumference of 100 mm. The pulmonary trunk and the right and left pulmonary arteries are normal.

The left atrium is not dilated and receives 4 normal pulmonary veins. The left atrial appendage is normal and does not contain any thrombus. The mitral valve is composed of 2 leaflets and has a circumference of 125 mm. The mitral valve leaflets appear normal and no hooding or regurgitation is noted. The mitral valve drains to the left ventricle. The left ventricle shows possible dilatation. The left ventricular free wall thickness is 16mm. The myocardium is uniform with no sign of acute ischaemia. The interventricular septum is 14 mm thick. There is a cream-yellow 8 mm lesion, possibly representing scar tissue, located at the posterior interventricular septum. No ventricular septal defect is noted. The left ventricular outflow tract is partially membranous. The aortic valve is composed of 3 normal leaflets and measures 92 mm circumference.

There is significant coronary artery atherosclerosis present within all 3 coronary arteries, as follows: right coronary 30% stenosis, left anterior descending 40% stenosis, left circumflex up to 60% stenosis. The left coronary artery is dominant. No thrombus is seen.

The thoracic aorta and its branches show mild uncomplicated atheroma. The abdominal aorta shows mild uncomplicated atheroma. The superior and inferior caval veins are normal. The portal vein is normal with no evidence of thrombosis.

Respiratory System

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Both lungs are red, solid, airless and heavy; the right lung weighs 1140g (expected = 450g) and the left lung 990g (expected = 400g). There are moderate bilateral pleural effusions comprising of 225mL haemoserous fluid. The external surface of the lungs shows prominent carbon pigment in a net-like pattern. There is are a few 2cm bullae located at the diaphragmatic surface of the left lower lobe.

The cut surfaces of the lungs show congestion, oedema, haemorrhage, fibrosis and cystic lesions. These changes diffusely affect both lungs. The cysts are most prominent in the lower zones of the upper lobes, bilaterally. No convincing consolidation is seen. (The tissue is showing considereble post-mortem autolysis.)

Peribronchial and hilar lymph nodes appear slightly enlarged. The pulmonary arteries show no sign of thromboembolus.

The trachea and main bronchi appear normal. The mucosa of the upper airways appears red and oedematous.

Gastrointestinal System
There is no ascites noted. The oesophagus and gastro-oesophageal junction appear normal. The stomach contains food material and the mucosa appears normal. No ulceration is seen. The mucosa within the duodenum appears normal. The small and large bowels have not been opened but have a normal external surface.

Hepatobiliary System
The liver weighs 1750g (expected = up to 1600g) and shows normal lobation. The liver has a normal shape. The cut surface appears slightly yellow. No masses or focal lesions are seen in the liver. There is no macroscopic evidence of steatosis or cirrhosis. The gall bladder is present and drains green bile. No cholelithiasis is noted. The pancreas appears normal along its entire length and there is no evidence of pancreatitis or other mass lesions.

Urogenital System
The right kidney weighs 190 grams and the left kidney weighs 210 grams. Both kidneys are normal weight and have normal appearance externally. The cut surfaces show normal corticomedullary pattern. No focal lesions are seen. The pelvicalyceal system and ureters are normal. The bladder and testes in the correction anatomical locations (but had not been further examined).

Endocrine System
The thyroid appears diffusely enlarged and weighs 30g. On cut section no focal lesions are identified. The adrenal glands appear normal and one adrenal gland (laterality uncertain due to autopsy processing) appears to have a well circumscribed 5mm yellow lesion which has been sampled for microscopy. The

pituitary is not examined.

Haematopoietic System
The spleen has a normal shape and location but is slightly large, at 230g (expected = up to 150g). The perihilar and mediastinal lymph nodes appear slightly enlarged. A very large subcarinal node is noted and sampled for histology. The cut surface is uniform.

Musculoskeletal system
The musculoskeletal system has not been extensively examined and appears grossly normal.

Central Nervous System
The brain has not been examined.

Block Key
1A-C LUL; 1D L lingula; 1E-F LLL; 1G-H RUL; 1I-J RML; 1K-L RLL; 1M thyroid; 1N-P liver; 1Q spleen; 1R-U Adrenal (R is one side); 1V subcarinal lymph node; 1W-X kidney; 1Y pancreas; 1Z Left circumflex artery; 1AA Left anterior descending artery; 1AB LV anterior wall; 1AC LV lateral; 1AD LV posterior wall; 1AE RV free wall; 1AF IVS; 1AG posterior IVS with possible scar.

PROVISIONAL MACROSCOPIC FINDINGS
Pulmonary fibrosis with a diffuse cystic, haemorrhagic pattern
Pulmonary oedema
Pleural effusions
Perihilar lymphadenopathy
Mildly dilated left heart
Possible myocardial scar
Possible adrenal cortical adenoma
Yellow liver
Goitre
Splenomegaly (mild)

Registrar: Dr A Dziouba
Pathologist: Dr A Dettrick
Pathology Queensland
Reported 19 October 2021

MICROSCOPIC
There is moderate autolysis of all tissues, consistent with the long period of time between the death and the autopsy. This does limit the histological assessment to some extent.

Cardiovascular system:

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Heart: There appears to be individual cardiac myocyte hypertrophy although assessing the extent of this is limited by post mortem change. This appears to be associated with small focal areas of interstitial fibrosis. There are also small foci of inflammation including some neutrophils, lymphocytes and macrophages. Rare Anitschkow cells are seen but definite granulomas are not seen. There is a scar where the posterior interventricular septum meets the left ventricular free wall. It is old. There is moderate to severe atherosclerosis affecting the coronary arteries as follows: Left circumflex coronary artery up to 70% stenosis; left anterior descending up to 50% stenosis.

Respiratory system:
Lungs:

Assessment of the lungs is difficult. On the one hand, it is limited by the degree of post mortem change and on the other, there are mixed features present.

The lung architecture is abnormal due to emphysema with extensive small bulla. In addition, foci of squamous metaplasia are present and there are some peripheral areas with well-established interstitial fibrosis in a pattern reminiscent of smoking-related interstitial fibrosis. All these changes are consistent with the history of smoking and emphysema/chronic obstructive pulmonary disease. Smokers macrophages will be mentioned below.

Superimposed on this background, there are other changes which are not compatible with uncomplicated emphysema.

These include areas of diffuse alveoli damage with hyaline membranes.

There are numerous airspace and interstitial granulomas. The granulomas tend to be well-formed and contain giant cells. Many of the giant cells contain cholesterol clefts and other features which are most suggestive of foreign body type giant cells.

There is an extensive although patchy pattern of alveolar macrophages, which in some areas are filling the alveoli in a pattern consistent with respiratory bronchiolitis. The alveolar macrophages are often pigmented and/or have foamy cytoplasm.

Plugs of organising fibrous tissue are present in airspaces (Masson bodies or the organising pneumonia pattern). This is a patchy process.

The inflammatory pattern also includes patchy areas of interstitial lymphocytes and occasional neutrophils. Airway neutrophils do not appear to be a feature.

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There is marked pulmonary oedema. There is also focal interstitial oedema, most prominently seen in occasional wide septa.

There are sloughed cells within airspaces that probably represent enlarged reactive type 2 pneumocytes. Sometimes these cells are binucleated, occasionally trinucleated and also multinucleated. No definite viral cytopathic changes have been identified although the poor preservation of tissue is a limiting factor in this assessment.

Two small pulmonary thromboemboli are noted. These are small and not associated with convincing infarcts. They are unlikely to be highly significant.

Gastro-intestinal system:
Liver: There is centrilobular congestion in keeping with heart failure. The architecture appears to be intact. Mild macro vesicular steatosis is present. No significant inflammation is seen. No focal lesions are seen. Further assessment is precluded by autolysis.
Pancreas: Post-mortem autolysis is severe and precludes assessment.

Endocrine system:
Thyroid: Multinodular goitre is confirmed.
Adrenals: There is a suggestion of bilateral nodular adrenal cortical hyperplasia. No definite adrenal cortical adenoma is seen. Unfortunately, due to post-mortem autolysis, obtaining an accurate weight of the gland was not possible. No focal lesions are seen.

Urogenital system:
Kidneys: Autolysis is marked. There are occasional globally sclerosed glomeruli which occasionally are associated with some chronic inflammation. Occasional protein casts are seen. Most of the glomeruli appear to be normal. The tubules cannot be reliably assessed due to post-mortem change.

Haematopoietic system:
Spleen: Normal.
Bone marrow:
Lymph nodes: In the mediastinal lymph node sampled, there is some follicular hyperplasia, congestion and dilation of sinusoids with macrophages. Other lymph nodes from elsewhere in the body are within normal limits.

MICROBIOLOGY
Respiratory virus PCR:
1. Left lung: Human Metapneumovirus DETECTED - but see NOTE below.
2. Right lung: Not detected.
NOTE: The result of the viral PCR has been discussed with a microbiologist

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(CH). The value was extremely low and likely to be a false negative.

Culture:
Right and Left lung: no significant growth.

FINAL AUTOPSY DIAGNOSES
Acute Lung Injury:
- Severe pulmonary oedema
- Diffuse alveolar damage
- Organising pneumonia-pattern
- Small pulmonary thromboemboli

Subacute and Chronic lung disease:
- Interstitial lung disease most in keeping with Respiratory Bronchiolitis
- Emphysema/chronic obstructive pulmonary disease

Ischaemic heart disease:
- Moderate to severe coronary artery atherosclerosis
- Small myocardial scar
- Subtle dilated cardiomyopathy pattern in keeping with ischaemic cardiomyopathy
- Likely congestive cardiac failure

Multinodular goitre

CAUSE OF DEATH
Acute lung injury/pulmonary oedema superimposed on chronic lung disease.

COMMENT
Autopsy pathology is often an exercise in balancing probabilities, weighing various findings to decide which is most significant and the likely sequence of inter-related components. That is certainly true in this case. Delay in autopsy has resulted in poor quality histology which complicates the assessment. With these provisos, the following comments can be made with reasonable confidence.

The lung pathology is severe and clearly the cause of death. The most outstanding finding in the lung is severe pulmonary oedema. Mixed early and late phase diffuse alveolar damage (DAD) with hyaline membranes and fibroblastic proliferation (or organising phase) is present. Squamous metaplasia is present. All of these may be part of the spectrum of pulmonary oedema. The small pulmonary thromboemboli are unlikely to be significant. In the background of the lungs, there is established emphysema.

The antemortem CT imaging has been reviewed and it shows extensive emphysema but also ground glass opacities in the remaining non-cystic lung. This would be consistent with Respiratory Bronchiolitis (RB) or pulmonary oedema, or both in this case. Importantly, the degree of fluid overload required to push such

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lungs into failure would be small, as there was little physiological reserve. The history of declining exercise tolerance for years and 3 weeks of worsening shortness of breath appears to fit.

It is difficult to be certain if there was a chronic component of RB-interstitial lung disease as a separate entity to emphysema and perhaps it does not matter as both are an expression of chronic lung disease due to smoking. RB-ILD may persist after cessation of smoking however the decedent stopped smoking 10y ago. There are ongoing collections of abundant foamy and pigmented alveolar macrophages which are significant in view of the discussion below.

The role of ischaemic heart disease and heart failure is unclear but not likely to be predominant. The heart was only mildly enlarged, the histological changes in the myocardium only mild and antemortem imaging showed normal size heart (if it was in severe failure, it would typically be enlarged).

The clinical suspicion of infective pneumonia is noted but there is no convincing evidence of lung infection found at autopsy. The inflammatory pattern in the lungs is not particularly suggestive of any specific infection with only scant neutrophils and small numbers of lymphocytes. Autopsy viral PCR was negative (false-positive result noted), autopsy lung culture was negative and blood cultures were negative. Human metapneumovirus PCR was technically 'positive' on 1 of 2 post-mortem lung samples but the read was extremely low and the result is highly likely to be a false positive. Viral PCR antemortem was negative. Therefore, lung infection has largely been excluded.

Regarding the lung granulomas seen at autopsy, many of these are clearly peribronchial and likely to be of the foreign body-type. These features are consistent with a reaction to an inhaled agent.

The causes of pulmonary oedema can be broadly divided into cardiogenic and non-cardiogenic. There is evidence of a component of heart failure in this patient. However, the list of causes of non-cardiogenic pulmonary oedema includes toxic inhalation and there is enough evidence in this case to suggest this is a likely cause of pulmonary oedema.

The United States Centres for Disease Control and Prevention (CDC) has recently provided a definition of E-cigarette or Vaping product use-Associated Lung Injury (EVALI).
This definition emerged out of the United States in 2019 following an outbreak in that country. Paraphrasing the CDC definition of EVALI: Use of vaping during the 90 days before onset AND ground glass opacities on CT AND negative testing for infection AND no evidence of alternative plausible diagnoses. A case that meets all these criteria is considered a confirmed case; a case that

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meets most of the criteria is a probable case.

A limited number of publications have appeared over recent years describing the pathological findings of EVALI, predominantly antemortam but also including a limited number of autopsy cases. These reports have attempted to define the clinical and pathological spectrum of this emerging disease. To date, no specific pathologic features for EVALI have been identified and it remains a diagnosis of exclusion which requires clinicopathologic correlation. Lung biopsies have shown a spectrum of non-specific acute lung injury patterns including accumulation of foamy and/or pigmented macrophages (most cases), organising pneumonia and diffuse alveolar damage, inter alia. These 3 features are present in the current case.

Most of the reports show no granulomas or definite features of hypersensitivity pneumonitis. There are contradictory reports that mention granulomatous pneumonitis (Layden et al NEJM 2019) or giant cell interstitial pneumonia (Fels Elliott et al Eur Repir J 2019). It is tempting to add together the findings of organising pneumonia, granulomas and some interstitial lymphocytes and conclude that these features would support a diagnosis of hypersensitivity pneumonitis however the pattern is far from classic for this entity (the granulomas are too well-formed and appear to be of the foreign body type and the organising pneumonia is too patchy). If further certainly about the nature of the inhaled agents were required, energy-dispersive spectroscopy may be requested, but this seems unnecessary at this stage.

Most of those cases reported in the US in 2019 related to vaping substances that contained cannabinoids and often 'grey market' or 'black market' suppliers. It is unknown what type of products the decedent was using or from where they were obtained.

This case meets the first three CDC criteria for EVALI. It is harder to be definite about the final criterion, for the various reasons discussed above. In conclusion, this case is a probable case of EVALI.

Registrar: Dr A Dzioube
Pathologist: Dr A Dettrick
Pathology Queensland
Reported: 17 November 2021

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T-28000 M-40000 M-78000