

The challenges of patients with complex comorbidity: it's all in the history

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Abstract

We present an autopsy case highlighting the challenges of post mortem in patients with complex comorbidity. The importance of reviewing investigations, previous results and clinical history is emphasised and important tips for trainees are discussed.

Keywords autopsy; cardiac; chemotherapy; myocardial fibrosis

Case report

A female patient in her mid-70s was referred for a post mortem via the coronial system. She had a known history of previous breast cancer which had been successfully treated with mastectomy and chemoradiotherapy but had otherwise been previously fit and well. For a few months prior to death, the patient had been suffering with dysphagia and had undergone investigations which identified gastritis and a hiatus hernia, for which she was given treatment. Despite this action, she continued to lose weight rapidly (reportedly over 2 stone in a 6-week period) and was therefore admitted to hospital for further investigation. Cross-sectional imaging (CT- and PET-scanning) revealed no malignancy in either the chest or abdomen and, whilst admitted, the patient had a seizure-like episode and so a CT scan of her brain was performed which was also reported as negative for significant pathology. Sadly, she deteriorated and was deemed for end-of-life care only and hence she died without a unifying diagnosis and with no cause of death available.

Relevant post mortem findings are outlined below; unless otherwise stated, all other findings were unremarkable.

External examination:

- Subcutaneous syringe pump cannula in situ in abdominal wall
- Right sided mastectomy scar with no evidence of recurrence

Cardiovascular system:

- Heart weight 360 g
- Moderate atheroma (75% stenosis) of the left anterior descending artery, rest within normal limits
- Moderate atheroma of the aorta

Respiratory system:

- Bilateral pulmonary oedema

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- Consolidation and frank pus in the left upper lobe
- Genitourinary system:

- Granular appearance to kidneys (bilaterally)

Toxicology samples were submitted and confirmed the presence of morphine at a level consistent with chronic therapeutic use as seen in the palliative care setting.

Histological samples were retained to determine the cause of death and the lung histology is shown in [Figure 1](#). This confirmed the presence of acute bronchitis and pneumonia in the left upper lobe and pulmonary oedema elsewhere.

Due to the history of recent seizure activity, the brain was retained with the permission of the coroner and was fixed for dissection and examination by our local neuropathology team. This was reported as showing a thin film of infiltrating cells over all parts of the brain surface and over the cranial nerve roots. These cells were medium-sized and had sparse cytoplasm and irregularly shaped hyperchromatic nuclei ([Figure 2](#)). Immunohistochemistry testing revealed these cells to be immunopositive for HMWCK and BerEP4 (focally) and immunonegative for CD3, CD22, CD45, CD56, ER, PR and GCDFFP-15. Review of the patient's original mastectomy histology was performed and the conclusion made that appearances were "consistent with a diagnosis of metastatic spread from her known pleomorphic lobular breast cancer".

Review of the histology from the heart ([Figure 3](#)) unexpectedly showed features of prominent patchy established fibrosis (visible even at low power) which was present in all the sampled tissue, from both the right and left ventricle. This fibrosis was not typical of the localised fibrosis seen with ischaemia and instead was more consistent with scarring following a diffuse process such as myocarditis. Although a clinically silent global myocarditis was considered (and deemed unlikely), review of the patient's notes revealed that she had recently been referred for investigation of an episode of dizziness and cardiac palpitations. These investigations had not been undertaken prior to deterioration but it was noted that the patient's post-surgery chemotherapy regime had included epirubicin, an anthracycline known to cause myocardial damage.

In light of the complex pathology found at post mortem, a detailed clinicopathological correlation was provided addressing the possibilities that the "seizure-activity" could have been related to leptomeningeal involvement by malignancy, or could instead have been related to a cardiac arrhythmic event secondary to myocardial fibrosis. We also outlined that the dysphagia (and possible aspiration pneumonia) may have been secondary to cranial nerve involvement by metastatic cancer. Finally, cardiac compromise and ventricular failure may have resulted in the bilateral pulmonary oedema seen at autopsy, which would also have increased susceptibility to pneumonia. The cause of death

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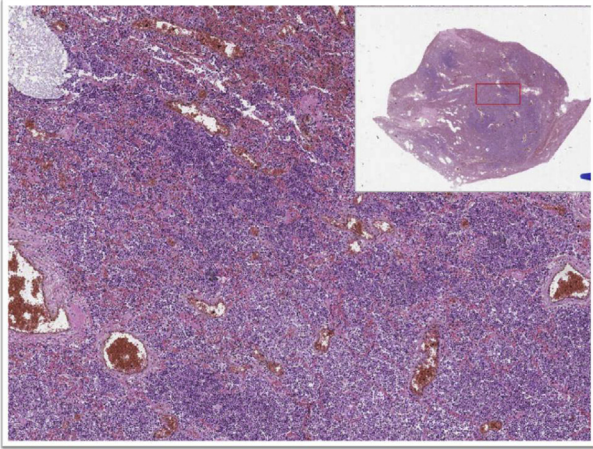


Figure 1 Histology from the upper lobe of the left lung showing consolidation with neutrophil polymorph infiltration and oedema.

was given as 1a. Acute bronchitis and bronchopneumonia, 1b. Metastatic leptomeningeal carcinomatosis, 1c. Pleomorphic/lobular right breast cancer (treated), 2. Myocardial fibrosis.

Discussion

Post mortem examination of elderly patients is often challenging because of the presence of multiple comorbidities and complex pathologies which may seem difficult to unify into a single cause of death. This case illustrates many of these challenges and

highlights the importance of access to, and review of, clinical notes, investigations and previous results. Our patient presented with symptoms suggestive of disseminated malignancy, but initial investigations in life had been negative, and a witness account of "new" symptoms (possible seizures) was difficult to confirm.

In the context of a normal head CT scan, and indeed normal macroscopic appearance of the brain, some pathologists may have chosen not to retain the brain for specialist examination. This would have resulted in the diagnosis of leptomeningeal carcinomatosis being missed, and we would urge trainees to follow the College guidance on sudden deaths in epilepsy¹ and to discuss organ retention with the Coroner in all relevant cases.

This case also reinforces the importance of a comprehensive drug history including current medications, illicit drug use and also, as in this case, significant previous drug treatments. Epirubicin is an anthracycline-type chemotherapy agent with both cytostatic and cytotoxic actions. A number of authors have reported significant cardiotoxicity, including impaired contractility and fibrosis, with the use of this drug^{2,3} and the FDA states that epirubicin, especially in combination with radiotherapy,⁴ may lead to an increased risk of congestive heart failure and an accelerated course to death.⁵ Other cardiovascular adverse events reported with epirubicin use in clinical trials include ventricular tachycardias, AV block, bradycardia and thromboembolism. Trainees should not feel pressured to either start cases or indeed to authorise their release until all relevant clinical information can be reviewed and synthesised in the context of the circumstances of death.

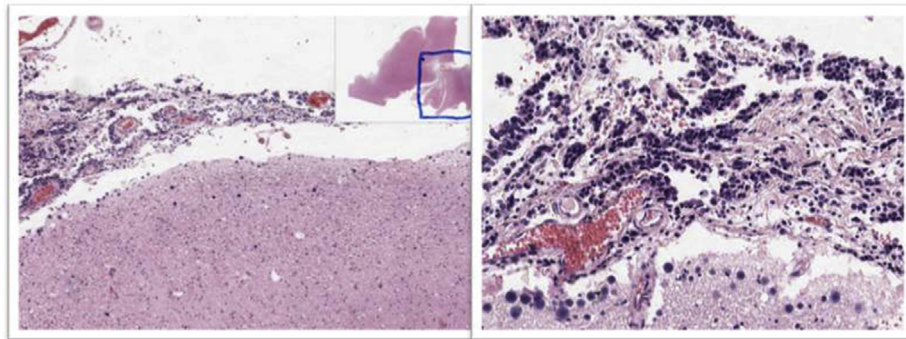


Figure 2 Histology from the brain showing film of infiltration by medium-sized cells with sparse cytoplasm and hyperchromatic nuclei.

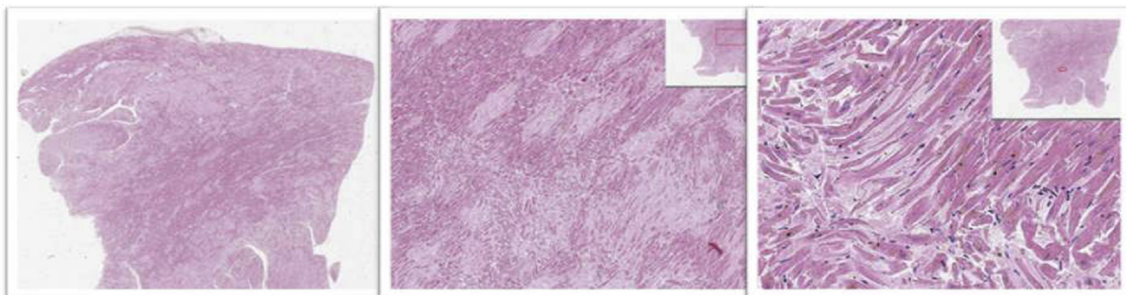


Figure 3 Histology from the heart showing widespread patchy established fibrosis with no evidence of infarction.

Conclusion

This case highlights some of the many challenges of autopsy pathology in the comorbid patient and emphasises the importance of reviewing all aspects of the clinical case prior to post mortem examination, and again in the context of the post mortem findings. Many of the solutions to these challenges are similar to those described by Burton in the context of the autopsy of post-surgical patients⁶ and we would direct trainees to his excellent review for more guidance. Finally, this case highlights the cardiotoxic effects of anthracyclines and emphasises the importance of autopsy pathologists maintaining their pharmacology knowledge and keeping abreast of new therapeutics and their potential side effects. ◆

Practice points

- Co-morbid patients present significant challenges at autopsy and a detailed clinicopathological correlation may be required to adequately explain all findings
- Epirubicin is an anthracycline known to cause cardiac toxicity including fibrosis and ventricular dysfunction
- Retention of the brain should be *considered* in all cases with a history of seizures, even in the context of normal neuroimaging

Multiple-choice questions

1. Which of these are anthracycline-type chemotherapy agents?

- Doxorubicin
- Epirubicin
- Idarubicin
- All of the above

Answer D. All of the above.

2. Which of these is the correct definition of SUDEP (sudden unexpected death in epilepsy)

- Death during documented status epilepticus (defined as unremitting seizure activity for > 30 min)
- Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, where necropsy examination does not reveal a toxicological or anatomical cause of death
- Sudden, witnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with evidence for a seizure lasting > 30 min, where necropsy examination does not reveal a toxicological or anatomical cause of death

D. Sudden, unexpected, witnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with evidence for a seizure, and excluding documented status epilepticus, where necropsy examination does not reveal a toxicological or anatomical cause of death

Answer B. Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, where necropsy examination does not reveal a toxicological or anatomical cause of death.

3. Which of these adverse effects has been reported with epirubicin use?

- Cardiac arrhythmias
- Hypertension
- Renal fibrosis
- Coronary thrombosis

Answer A. Cardiac arrhythmias.

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