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Early View

Research letter

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Amber Louw, Calvin Sidhu, Deirdre B. Fitzgerald, Jenette Creaney, Siaw Ming Chai, Y.C. Gary Lee

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Clump material within drainage chest tubes contain diagnostic information: A proof-of-concept case series

Amber LOUW [1,2,3,4]	BSc MBBS ALOUW@our.ecu.edu.au
Calvin SIDHU [4]	MBBS FRACP caljitsid@gmail.com
Deirdre B. FITZGERALD [4,5,6]	MBChB BAO MRCP Deirdre.Fitzgerald@health.wa.gov.au
Jenette CREANEY [3,4,6]	PhD jenette.creaney@uwa.edu.au
Siaw Ming CHAI [1]	MBBS MMSc FRCPA Siaw.Chai@health.wa.gov.au
Y. C. Gary LEE [4,5,6]	MBChB PhD FRACP FRCP FCCP gary.lee@uwa.edu.au

***Affiliations**:*

1. Department of Anatomical Pathology, PathWest Laboratory Medicine, Queen Elizabeth II Medical Centre, Nedlands, Western Australia
2. School of Medical and Health Sciences, Edith Cowan University, Perth, Australia
3. National Centre for Asbestos Related Disease, University of Western Australia
4. Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia
5. Medical School, University of Western Australia
6. Institute for Respiratory Health, Western Australia, Australia

Correspondence: Prof Y C Gary LEE, UWA Medical School, 533 Harry Perkins Bldg, QEII Med Ctr, Perth, WA 6009, Australia. Tel: +61 8 61510913 Fax: +61 8 6457 1555

To the Editor:

Pleural effusion is a common diagnostic and therapeutic challenge[1,2]. Malignant pleural effusion (MPE), in particular, often necessitates fluid drainage with chest tubes for symptom control[3,4] and its diagnosis requires cyto-histological assessment of pleural fluid or tissue biopsies[2].

Clumps of material are commonly observed within the chest tube following insertion and fluid drainage. These are often considered an irrelevant nuisance as they may block fluid drainage and often require removal by flushing of the tube to restore patency. The nature and constituents of this 'clump material' has never been formally studied. As they are dislodged from the pleural cavity after tube insertion, we hypothesized that their contents may potentially provide valuable diagnostic material.

This prospective, single-centred, proof-of-principle study examined the histological composition, and any added diagnostic information, of the clumps collected from within the lumen of intercostal chest tubes (n=10) or indwelling pleural catheters (IPC, n=10) of patients with known or suspected pleural malignancies. The clumps were removed in a variety of ways depending on individual circumstances, particularly the drainage device used. Essentially, clumps were removed as they would be in daily clinical practice should they block the chest tube or IPC. Most commonly, the tube was disconnected from the underwater seal bottle to allow the clump to be dislodged from the tube (by gravity) into a sterile container. The samples were transported in sterile containers, usually bathed in the patients' own pleural fluid, and processed at the PathWest Laboratory Medicine, QEII Medical Centre, Western Australia. Where more than one specimen was submitted per patient, the first was analysed. All patients provided informed consent (Sir Charles Gairdner HREC approval #RGS0000001517).

Over the 10-month period beginning January 2019, 20 'clump' samples were collected from 20 cancer patients who underwent chest tube or IPC drainage for known or suspected MPE (mean age 68.3 years; nine were female). Their underlying cancers included mesothelioma (n=8), non-small cell lung cancer (n=4), gynaecological carcinomas (n=3), sarcoma (n=2),

and small cell lung cancer, breast carcinoma, and chronic lymphocytic leukaemia (CLL) (n=1 each). Twelve patients had malignant cells in prior pleural fluid samples.

In all cases the entire specimen was submitted for microscopic examination, separate from any pleural fluid, by two pathologists (AL and SMC). The samples were formalin fixed, paraffin embedded and 4μm sections were cut from each block and stained with haematoxylin and eosin (H&E). Additional immunohistochemical and special stains were performed as appropriate to assess each specimen for (i) constituents of the background material e.g. fibrin and talc; (ii) inflammatory cells, their subtypes, and pathogenic organisms and (iii) malignant cells.

On macroscopic examination the specimens consisted of fragments or tubular cream to brown material 30 to 260mm in maximal dimension. On microscopic assessment, the fragments consisted predominantly of fibrin with entrapped cellular material (see Figure 1). In some cases, the fibrin demonstrated features of organisation, with areas containing fibroblasts, haemosiderin deposition and haemosiderin-laden macrophages. The cells admixed within the fibrin included inflammatory cells, macrophages and, where present, atypical cells. All samples contained chronic inflammatory cells in the form of lymphocytes. In 14 cases acute inflammatory cells, namely neutrophils, were present and ranged in quantity from scattered to large numbers (in a post-medical thoracoscopy patient). Talc was present in the clump samples from all six patients with prior talc instillation. In two cases small numbers of bacteria were noted; neither had clinical evidence of infection and pleural fluid culture was negative.

Malignant cells were identified in 15 of 20 patients including all 12 cases who had previous cytologically confirmed MPEs. Malignant cells were present in variable amounts, ranging from a few scattered cells within the fibrin, to isolated cell clusters, to sheets of cancer cells. Malignancies identified included mesothelioma (5 epithelioid, 1 sarcomatoid, 1 biphasic), lung cancers (3 adenocarcinoma, 1 adeno-squamous carcinoma, 1 small cell neuroendocrine carcinoma), high grade serous carcinomas of tubo-ovarian origin (n=2) and angiosarcoma (n=1). In three patients, analysis of the clump material from the chest tube provided the first cytological evidence of MPE. For example, malignant cells were identified within the chest tube ‘clump material’ from a patient with a known history of right atrial angiosarcoma whose

pleural effusions were cytology negative on three previous occasions. Mesothelioma cells were also found in the clump material of a patient whose prior pleural fluid samples had consistently been cytology negative, and his diagnosis of sarcomatoid mesothelioma was based on pleural biopsy. Another patient with mesothelioma had no prior pleural fluid available for analyses, and his clump material was the first cytological evidence of mesothelioma.

In another two cases, atypical cells suspicious (but not definitive) of malignancy were found in the clump material. Atypical mesothelial cells were found in a patient with biopsy-proven epithelioid mesothelioma. The other patient, whose prior pleural fluid cytology was negative, had metastatic Ewing sarcoma; atypical cells were also identified in the clump material but were too degenerate for further workup to provide a definitive diagnosis. In the remaining three patients (with breast cancer, uterine adenocarcinoma and chronic lymphocytic leukemia) no malignant cells were identified in the clump samples; none had subsequent positive pleural cytology.

MPE affects an estimated 200,000 patients a year in the United States alone[1]. Diagnosis requires pleural fluid cytology and/or pleural biopsies via imaging guidance or even thoracoscopic surgery - procedures with costs and potential complications [2]. This study provides the first account of the nature of these commonly observed ‘clumps’ often seen within chest tubes after insertion. Clinicians traditionally view the clump material as undesirable material that block tube drainage.

This series provides proof-of-principle data to show that the clumps consists mainly of fibrin which provides a scaffold that traps cellular material (especially inflammatory and malignant cells) drained from the pleural cavity with the pleural fluid. In patients with pleural malignancies, cancer cells are often be found within the ‘clumps’ and are generally of sufficient quality to allow pathological analysis. Our samples covered a wide spectrum of malignancies including those commonly associated with MPE as well as cancers known to be difficult to diagnose by cytology (mesothelioma and angiosarcoma). In day-to-day clinical practice, these clumps often have to be flushed from the tube to restore drainage and can easily be collected to provide an additional source of diagnostic material.

Our series provides proof-of-concept information and has limitations. This is a small single-centred cohort of patients; most have known malignant pleural effusions. The viability of the clump samples, and best collection/processing methods for more advanced testing such as molecular genetics will require further investigation.

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***Conflict of Interests*:** None of the authors have any conflict of interests to declare.

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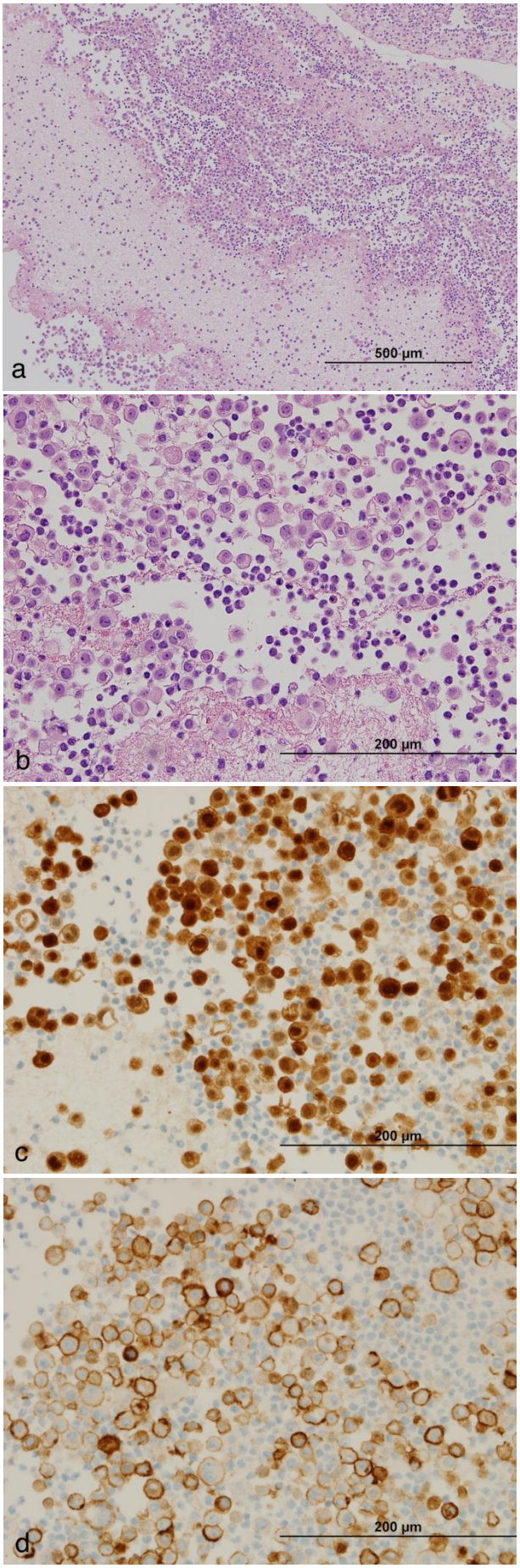
Figure 1. Representative sections of the clump material containing malignant mesothelioma, (a) low power view demonstrating inflammatory and malignant cells embedded within fibrin (H&E section, original magnification, x10, scale bar = 500 µm), (b) higher power view of this section demonstrating sheets of malignant cells with epithelioid morphology with large, moderately pleomorphic nuclei, prominent nucleoli and eosinophilic cytoplasm (H&E section, original magnification, x40, scale bar = 200 µm), (c) the atypical cells demonstrate strong cytoplasmic and occasional nuclear staining with calretinin (calretinin IHC, original magnification, x40, scale bar = 200 µm) and (d) the atypical cells demonstrate strong membranous staining for EMA (EMA IHC, original magnification, x40, scale bar = 200 µm).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