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Malignant mesothelioma cells with characteristic intracytoplasmic vacuolization and lipids

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Patient diagnosis: Satoshi Morito and Hiroshi Yasui. Writing-original draft: Satoshi Morito and Hiroyuki Ohsaki. Writing-review and editing: Hiroshi Yasui, Tomoo Itoh, Shingo Kamoshida and Hiroyuki Ohsaki. Supervision: Hiroyuki Ohsaki.

Data availability statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of patients but are available from the corresponding author [HO] upon reasonable request.

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Conflict of interest disclosure

The authors have no conflicts of interest to declare.

Ethics approval statement

This case report has been granted an exemption from ethics approval by the ethics committee of the Rakuwakai Otowa Hospital because written informed consent was obtained from the patient before his death.

Patient consent statement

Written informed consent was obtained from the patient before his death.

Abstract

In this brief report, we described some uncommon cytomorphological features of malignant mesothelioma (MM) cells in pleural effusions. The tumor cells exhibited abundant cytoplasmic vacuolization, with presence of single or multiple eccentric nuclei in several cells. In the Giemsa-stained smear, we observed a glossy spherical material in some cells which tested positive in Sudan III stain. In immunocytochemical analysis, tumor cells were positive for calretinin, podoplanin, epithelial membrane antigen, and methylthioadenosine phosphorylase; tumor cells were negative for BRCA1-associated protein 1, CD68, and desmin. The intracytoplasmic vacuoles were positive for adipophilin expression.

Key words: foamy cells, cytology, pleural effusion, malignant mesothelioma, lipids

1 | INTRODUCTION

Malignant mesothelioma (MM) is a rare tumor that arises from serosal membranes of the pleural, peritoneal, and pericardial cavities, and has a high incidence in middle-aged to elderly males. Asbestos exposure is the primary etiological factor for this tumor; genetic predisposition has also been reported as a cause of MM[1,2]. Epithelioid and mixed (biphasic) types of MM cells are likely to be present in cytological specimens, whereas, sarcomatoid and desmoplastic types are rare. The most recognizable pattern of MM cells are numerous clusters, formed along with non-cohesive tumor cells. These cells can be mononucleated, binucleated, or multinucleated, with a prominent nucleolus and dense cytoplasm[3].

Herein, we report a rare case of MM in which marked diffuse intracytoplasmic vacuolar foamy changes were observed in most MM cells. Periodic acid–Schiff and Sudan III staining of air-dried smears and immunocytochemistry using cell block specimens proved that the cause of these vacuoles were lipids.

2 | CASE REPORT

2-1 Case History

A male patient in his 80s, having a history of asbestos exposure and a 70-year smoking history, was admitted to our hospital for a right pneumothorax. His medical history included subdural hemorrhage, chronic obstructive pulmonary disease, type II diabetes, stage IV chronic kidney disease and prostate cancer. The patient's laboratory test results were as follows: blood urea nitrogen, 51.7 mg/dl; serum creatinine, 3.02 mg/dl; estimated glomerular filtration rate, 16; and blood glucose, 125 mg/dl. Computed tomography revealed pleural

effusion, pleural thickening, and bilateral pleural calcifications. However, the patient could not undergo pleural biopsy because of a severe systemic condition. Therefore, based on the cytomorphological and immunophenotypic features, the patient was diagnosed with epithelioid-type MM. The patient died of the disease three years after his first admission; autopsy was not performed.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The case report was granted an exemption from ethics approval, by the ethics committee of Rakuwakai Otowa Hospital, because written informed consent was obtained from the patient before his death.

2-2 Materials and Methods

For pleural effusion cytology, alcohol-fixed and air-dried samples were prepared and separately stained with Papanicolaou, Giemsa, Periodic acid–Schiff (PAS), and Sudan III stains. The cell blocks contained formalin-fixed cells. Sections from the cell block were stained with hematoxylin-eosin and subjected to immunocytochemical analysis for calretinin, podoplanin (D2-40), epithelial membrane antigen (EMA), methylthioadenosine phosphorylase (MTAP), BRCA1-associated protein 1 (BAP-1), CD68, desmin, and adipophilin; fluorescence *in situ* hybridization (FISH) was performed for 9p21. Cytological smears and cell block sections were observed under a polarizing microscope.

2-3 Results

Tumor cells observed in the cytological smears exhibited cytoplasmic vacuolization with one or more eccentric nuclei; however, large clusters were not observed (Fig. 1A). The

intracytoplasmic vacuoles were negative for PAS staining. In the Giemsa-stained smears, glossy spherical structures were observed in some tumor cells (Fig. 1B), which were positive for subsequent Sudan III staining (Fig. 1C). Hematoxylin-eosin-stained cell block sections showed that the tumor cells exhibited cytoplasmic vacuolization, similar to that observed in the cytological smears (Fig. 2A). Immunocytochemistry revealed that the tumor cells were positive for calretinin, D2-40, EMA, and MTAP, but negative for BAP-1, CD68, and desmin (Fig. 2B). The intracytoplasmic vacuoles of tumor cells were positive for adipophilin (Fig. 2C). FISH did not detect homozygous deletion of 9p21.

3 | DISCUSSION

In this case report, the tumor cells were dispersed and showed markedly diffused intracytoplasmic vacuolar foamy changes. Notably, some tumor cells with intracytoplasmic glossy spherical structures were identified in the Giemsa-stained smears, and these glossy structures were positive for Sudan III staining. This suggested the presence of lipids in such large amounts that they did not dissolve in methanol or xylene during Giemsa staining.

Nelson et al.[4] examined 15 cases of MM with cytoplasmic vacuoles using electron microscopy and found that large amounts of glycogen were present in seven cases, mixed glycogen and lipid in three, lipid-only in three, swollen mitochondria in one, and multilayered crystalloid material in one case. In our case study, the cells were negative for PAS staining, but positive for Sudan III staining and adipophilin immunoreactivity, suggesting that only lipids were present in the vacuoles. Spriggs et al.[5] reported three cases of MM cells with vacuoles that appeared on Giemsa-stained smears. However, immunocytochemistry and electron microscopy was not conducted for these cases, making it questionable whether or not the cells with vacuoles were

MM cells. Furthermore, as they reported that no MM cells with vacuoles were observed in the histological specimens, it is possible that the cells in the Giemsa smears were instead macrophages. There is also a report of tumor cells with vacuoles appearing in the fine-needle aspiration cytology of MM[6]; however, these vacuoles appeared large, single, and different in morphology from those observed in our case. Chang et al.[7] reported that MM cells with diffuse intracytoplasmic vacuolar foamy changes were found in cytologic smears and that Oil Red O staining and electron microscopic retrieval of surgical material subsequently revealed that the cytoplasmic vacuoles were caused by lipids. A few scattered cells or small clusters of cells indicative of clear cell cytoplasm are common in MM; however, epithelioid mesothelioma consisting mainly of tumor cells with diffuse vacuolar foamy change is rare[8]. Therefore, only a few case reports have been published on this; most of them are based on histological specimens[9–14], and only two cases[7], including ours, describe the cytomorphological findings in cytological smears. Although the mechanism underlying intracytoplasmic lipid accumulation in malignant mesotheliomas remains unclear, Takada et al.[15] reported intracytoplasmic lipid accumulation with diffuse vacuolar foamy changes in papillary thyroid carcinoma and suggested that these findings could be a degenerative change, and papillary growth may be involved in the pathogenesis. Indeed, all reported MM cases with intracytoplasmic lipid accumulation and/or diffuse vacuolar foamy changes showed a papillary structure[7,9–14].

Tumors with diffuse vacuolar foamy changes, similar to those seen in this case, may rarely occur at other sites, such as the thyroid[15], kidney[16], prostate[17], and pancreas[18]. Therefore, when tumor cells with diffuse vacuolar foamy changes are found in body fluid cytology, cytologists and cytopathologists should consider the possibility of MM and related tumors, and perform fat staining and immunocytochemistry.

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FIGURE LEGENDS

FIGURE 1

Pleural effusion smear. (A) Tumor cells with vacuolated cytoplasm (Papanicolaou stain, 400×). (B) Glossy spherical structures present in some tumor cells (arrow) (Giemsa staining, 1,000×). (C) The glossy structures were positive for Sudan III staining (Sudan III, 600×).

FIGURE 2

Cell block sections. (A) Tumor cells had a vacuolated cytoplasm, similar to cytologic smears (Hematoxylin-eosin, 400×). (B) Tumor cells were negative for CD68 (400×). (C) Tumor cells were positive for D2-40 (red); intracytoplasmic vacuoles were positive for adipophilin (brown) (400×)

Ohsaki H

Brief report

Fig. 1A

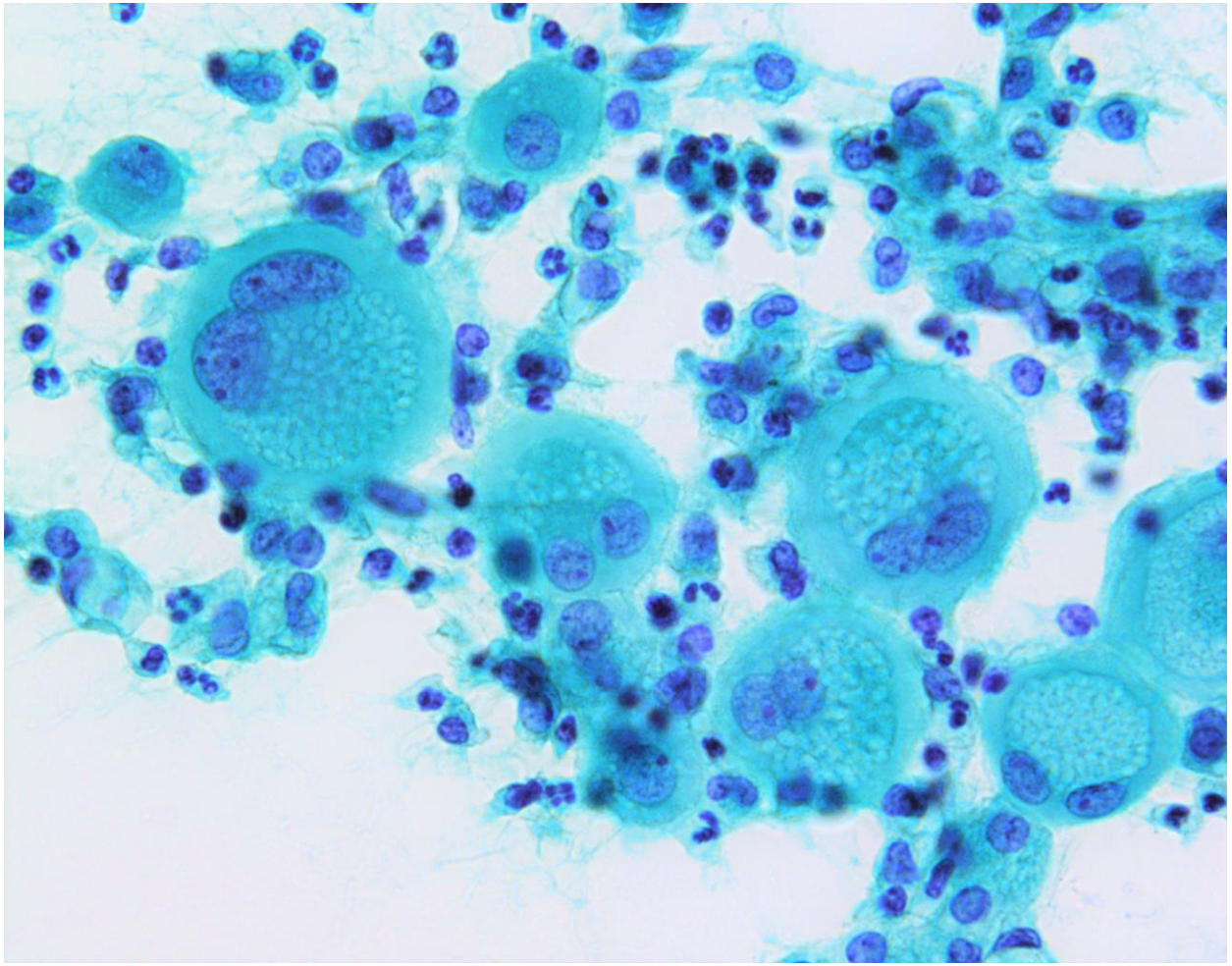

Fig. 1B

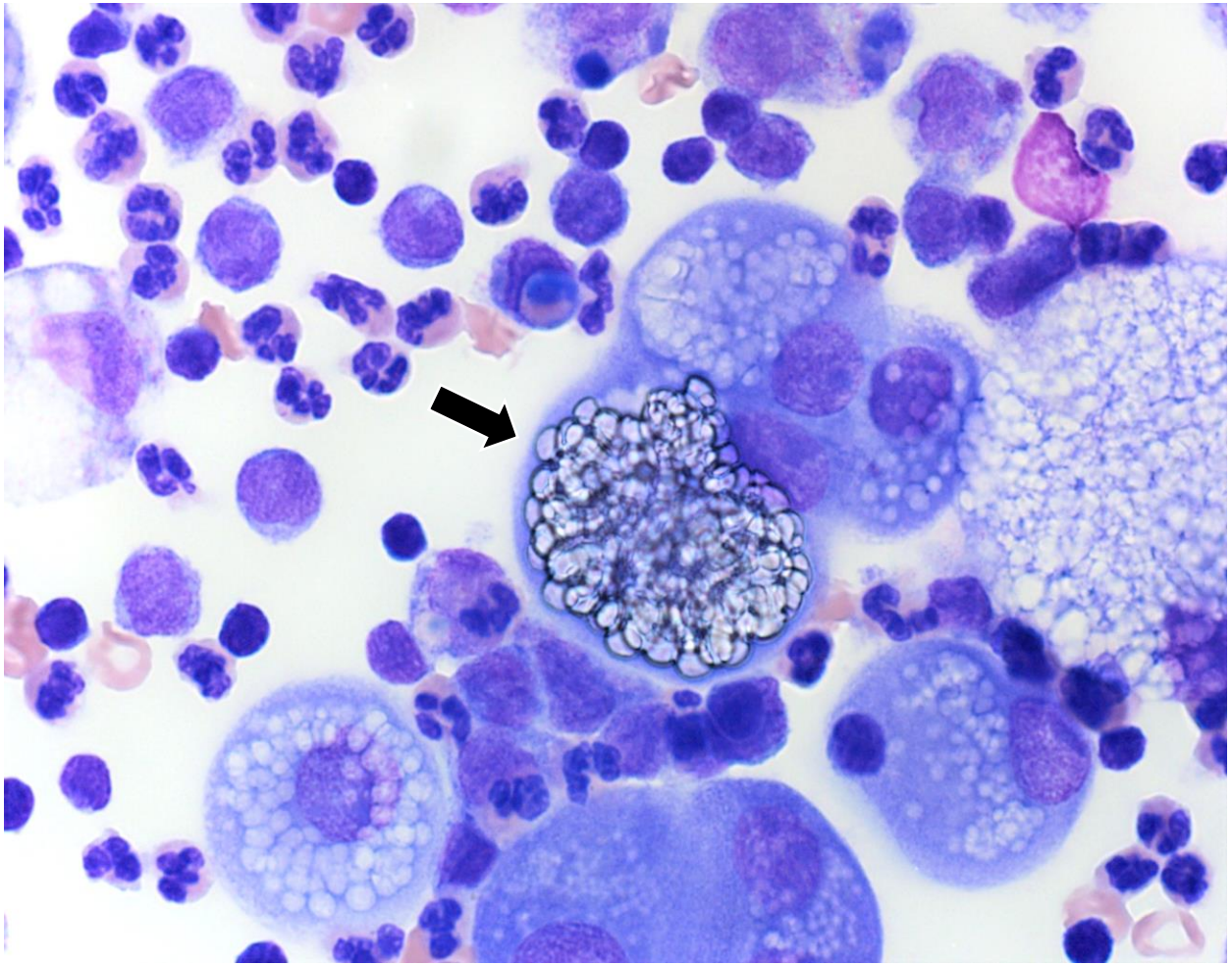

Fig. 1C

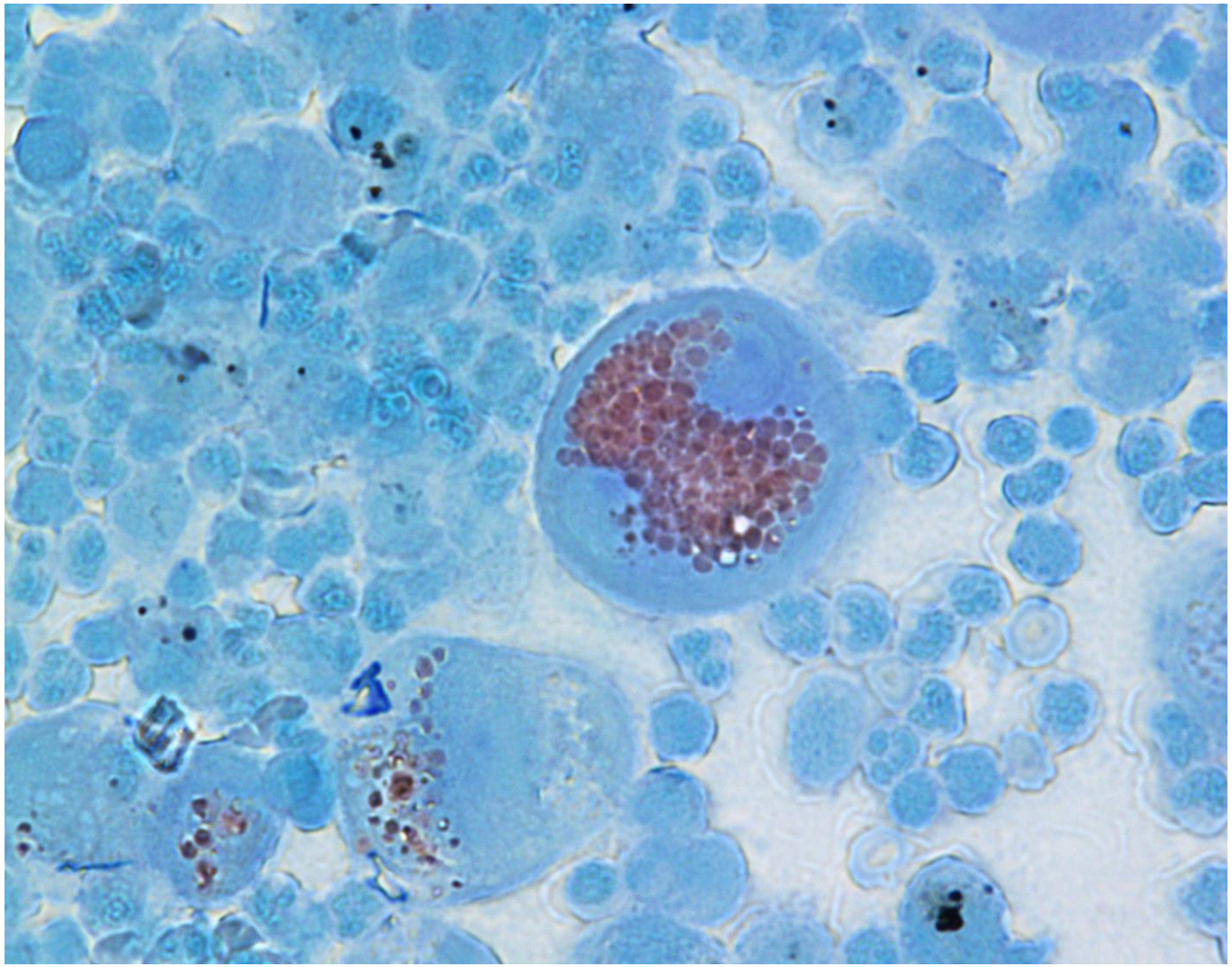

Fig. 2A

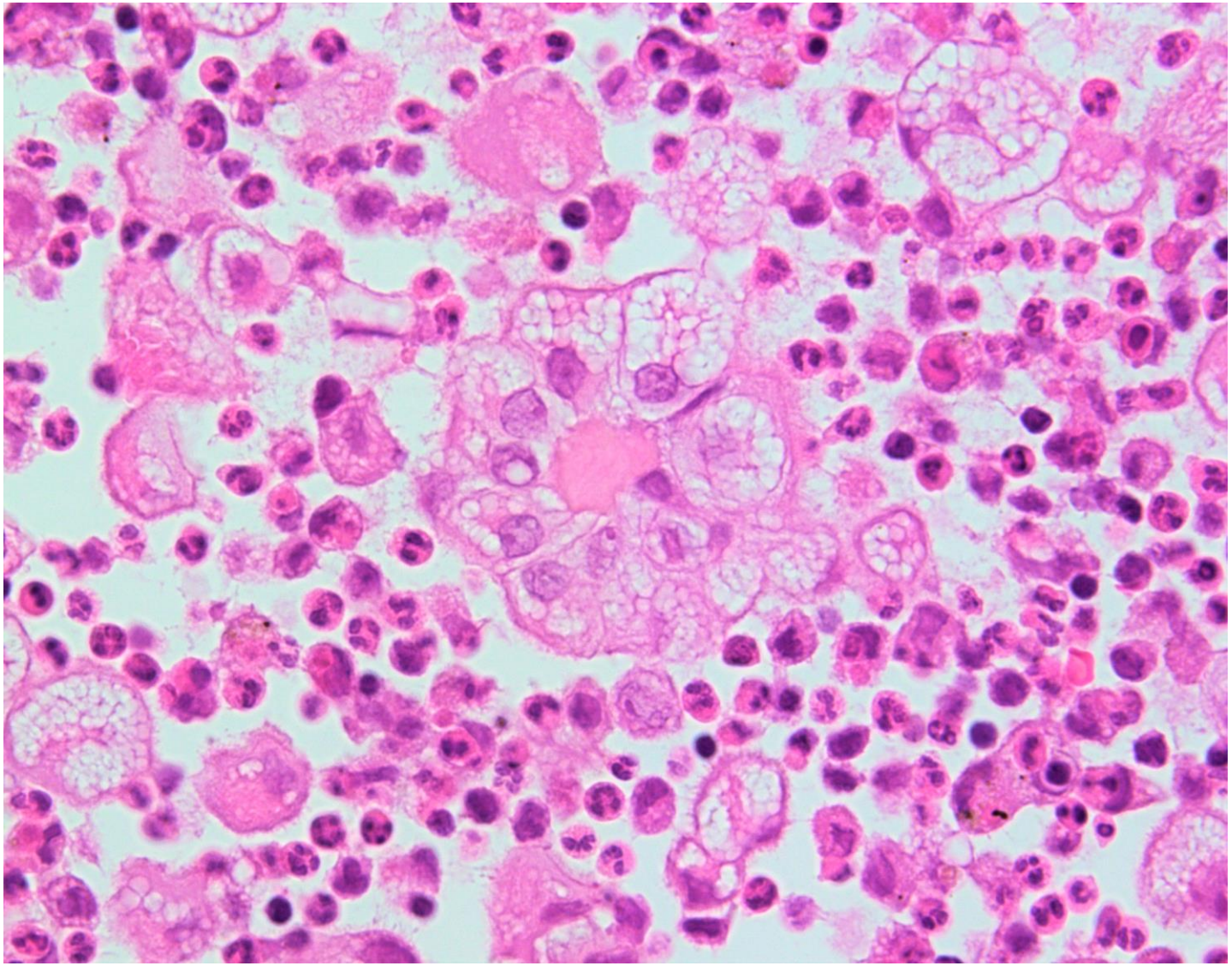

Fig. 2B

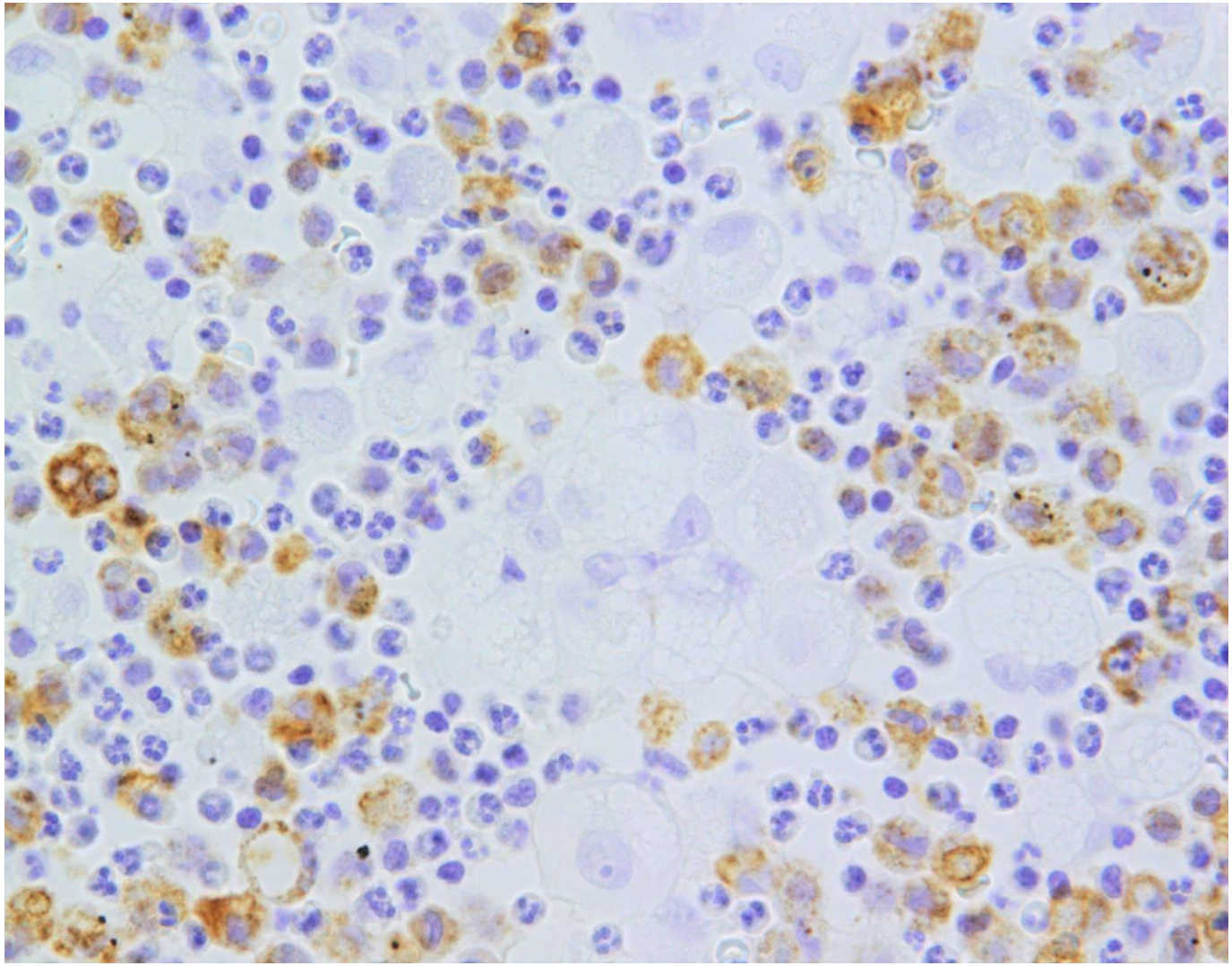

Fig. 2C