Asian Journal of Medicine and Health Sciences Vol 4 Issue 2 November 2021

CASE REPORT

Metastatic Pleural Malignancy Beyond Simplicity: A Case Report and Literature Review.

Myo Thet Tin[1], Ye Tun[2], Norain Karim[3] and Than Than Htwe[3]

[1]Department of Clinical Pathology, Yangon General Hospital, Myanmar.
[2] Department of Medicine, Yangon General Hospital, Myanmar.
[3] Discipline of Pathology, Preclinical-Based Department, Faculty of Medicine, University Kuala Lumpur – Royal College of Medicine Perak, Malaysia.

Corresponding Author
AP Dr. Than Than Htwe
UniKL Royal College of Medicine Perak, No. 3, Jalan Greentown, 30450 Ipoh, Malaysia.
Email: ththan@unikl.edu.my

Abstract

Pathologic involvement of the pleura presenting with pleural effusion is most often a secondary complication of some underlying diseases such as bacterial infection and neoplasm. Concerning neoplasm, it can be either a primary neoplasm: mesothelioma or a metastatic neoplasm. Secondary metastatic involvement is far more common than primary tumours. The most frequent metastatic malignancies arise from primary neoplasms of the lung and breast. In addition, malignancy from any organ of the body may spread to the pleural spaces such as ovarian carcinomas and metastatic lesions from the gastrointestinal tract, commonly cancer of the colon. In most metastatic involvements, a serous or serosanguineous effusion follows, that often contains neoplastic cells. For this reason, careful cytologic examination of the sediment is of considerable diagnostic value. It is also necessary to take pleural biopsy tissue together with diagnostic aspiration of pleural fluid for exclusion and confirmation of the most possible primary focus. Hence, the role of pathologist is a critical necessity in supporting appropriate clinical management of the patient. A case report and literature review is presented in this article, highlighting the value of immunohistochemistry and cytopathology in reaching to the final diagnosis.

Keywords: pulmonary malignancy, pleural effusion

Introduction

The diagnosis of the metastatic carcinoma of unknown origin can be very difficult. The determination of the primary site of the metastasis is a challenge to both oncologists and pathologists, having potentially important clinical and therapeutic consequences.[1-3] In the setting of carcinomas of unknown primary, clinicopathological correlation and a panel of standard immunohistochemical stains help define the primary site, and direct appropriate treatment.[4,5]

Case Report

A 64-year-old Myanmar lady presented with progressive cough and dyspnoea due to a left-sided pleural effusion. She was admitted to the Chest Unit of Yangon General Hospital (YGH). Clinical and radiological investigations of the case were suggestive of metastatic pleural effusion (MPE) with possible primary from the lungs. Aspiration of the pleural fluid together with pleural biopsy was performed and the specimens were sent to the Diagnostic Pathology Laboratory in YGH. About 35ml of deep straw-coloured pleural fluid was aspirated. Sediment smears of the pleural fluid were prepared for cytopathological study including Papanicolaou stain. Tissue slides were reviewed under conventional hematoxylin and eosin stain (H&E) for histopathology. A panel of immunohistochemistry (IHC) slides were also prepared with available immunostains including: CK-7 (clone OVTL 12/13, 1:50; DAKO), CK-20 (clone Ks20.8, 1:50; DAKO), WT1 (clone 6F-H2, 1:50; DAKO), Desmin (clone D3 Mo760, 1:50; DAKO), TTF-1 (8G7G3/1, 1:200; DAKO), CDX2 (clone AMT28, 1:50; DAKO), and P63 (4A4, 1:50; DAKO). After incubation, immunodetection was done with DAKO EnVision Visualisation Method (DAKO, Glostrup, Denmark), with diaminobenzidine chromogen as the substrate. Microscopic features of the Papanicolaou stained cytopathology smears revealed the presence of two populations of cells: one group of cells were adhering together in glandular clusters and another type of cells were dispersed individually having abundant cytoplasm (Figure 1A and 1B). H&E stained slides revealed pleomorphic cells adhering to the pleural tissue that were highly suspicious of metastatic non-small cell carcinoma of the left pleural with primary neoplasm elsewhere (Figure 2A). Further confirmation by IHC staining slides showed strong positive staining for CK-7, TTF-1 and WT-1 in the pleomorphic cells, weakly positive staining of non-pleomorphic cells for Desmin, but negative for CK-20 (Figure 2B-2F), CDX2 and P63.

Based on the morphological and immunohistochemistry findings, the case was confirmed as pleural metastasis of non-small cell lung cancer (NSCLC): adenocarcinoma primary from the lung excluding malignant mesothelioma as well as other primaries from the breast, ovary, and gastrointestinal tract.

Discussion

Metastatic adenocarcinoma from an unknown primary site is a common clinical problem [3,4]. It is important to find out the primary site of a metastatic carcinoma, for the purpose of getting effective treatment of choice for the patient. This is supported by getting a precise diagnosis, hence improving the overall outcome.[5] The histological assessment is often very helpful, but may not differentiate adequately between various primary tumours. Immunohistochemistry is the most common adjunctive method used in the analysis of the patient with cancer of unknown primary site.[6] Among the most useful cytokeratins are CK7 and CK20.[6] CK7 is found in many ductal and glandular epithelia, including lung, breast, ovary, and endometrium. [7-10] CK20 is expressed in the gastrointestinal (GI) epithelium, urothelium, and Merkel cells.[10] Desmin is known to be expressed in mesenchymal tumour component of pulmonary

and pleuropulmonary blastoma, sarcomatoid carcinoma, and salivary gland-type tumours arising in lung. However, desmin expression has not been reported in other types of primary lung cancers without mesenchymal tumour component. Desmin-positive primary lung cancers are rare. In the absence of skeletal muscle differentiation, desmin expression is observed exclusively in carcinomas with neuroendocrine differentiation, and most of them are high-grade carcinomas.[11] In our case, only a weak staining of desmin could exclude such malignancies. WT1 is expressed in malignant mesothelioma, peritoneal cancer and ovarian cancer (malignancy classification according to ICD-10). On the other hand, malignant mesothelioma, serous adenocarcinoma, mucinous cancer, signet ring cell carcinoma, carcinosarcoma and adenosarcoma (malignancy classification according to ICD-O-3) showed strong WT1 expressions.[12] In our case, WT1 is weakly stained only in those non-pleomorphic cells. As such, we can exclude the possibility of such malignancies.

The distinction of benign from malignant mesothelial proliferations in cytologic specimens can be problematic. The combination of positive EMA and negative desmin strongly favours malignant mesothelioma. Conversely, a combination of negative EMA and positive desmin favours a reactive process.[13] In this patient, the pleomorphic cells that were strongly positive for CK-7 and TTF-1 are in favour of adenocarcinoma of the primary lung tumour. TTF-1 reflects Nkx2 gene expression in the lungs. [14]

Weakly positive WT-1 and Desmin IHC in non-pleomorophic cells reflects the benign nature of mesothelial cells, thus ruled out malignant mesothelioma in this case. WT-1 reflects tumour suppressor gene mutation in ovarian cancer where it shows positive nuclear stain. It is also positive in stomach, prostate, biliary, urinary tract and in malignant melanoma as cytoplasmic stain. Hence, metastatic malignancy from these organs could also be excluded.
Moreover, CD-20 and CDX2 negative results in the pleomorphic cells ruled out colorectal cancer where CD-20 is a fairly specific marker for tumours of gastrointestinal tract origin. [15]

P63 is a well-known marker of squamous differentiation. Overexpression of this gene has been consistently identified in squamous cell carcinoma of the lungs by global gene expression profiling or by IHC [16–21]. Hence our findings for negative P63 stain exclude the primary squamous cell carcinoma of the lung. Staining for P63 was also negative in the pleomorphic cells. It is a prostate marker, and myoepithelial cells marker from the breast tissue. Hence, excluding such malignancies. Based on the morphological and immunohistochemistry findings, the case was confirmed as pleural metastasis from the non-small cell lung cancer (NSCLC): adenocarcinoma primary from the lung excluding malignant mesothelioma as well as other primaries from the ovary, colon.

Conclusion

A case report and literature review is presented in this article, highlighting the value of immunohistochemistry and cytopathology in reaching to the final diagnosis. Histological, cytological and immunohistochemical findings confirm the diagnosis of metastatic adenocarcinoma of lung, Left Pleura. Based on the morphological and immunohistochemistry findings, the case was confirmed as pleural metastasis from the non-small cell lung cancer (NSCLC): adenocarcinoma primary from the lung excluding malignant mesothelioma as well as other primaries from the ovary, colon.

Author Contributions

MTT performed the laboratory diagnostic investigation and confirmation of the case. YT performed the case investigation, management

and case review. NK performed the manuscript editing and review. TTH performed the concept, designing, literature search, manuscript preparation, editing and review.

Conflict of Interest

The authors declare no conflict of interest.

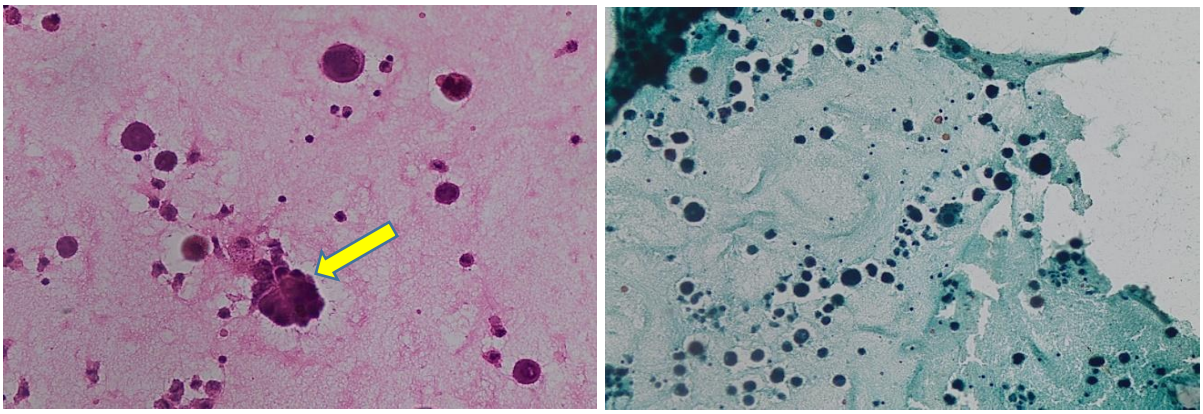

Fig.1A **Fig.1B**

Figure 1A & B. Cytopathology of the pleural effusion fluid in H&E stain revealed two population of cells: one group of cells adhering together in glandular cluster (yellow arrow) (Fig 1A) and another type of cells that were dispersed individually having abundant cytoplasm (Fig 1B).

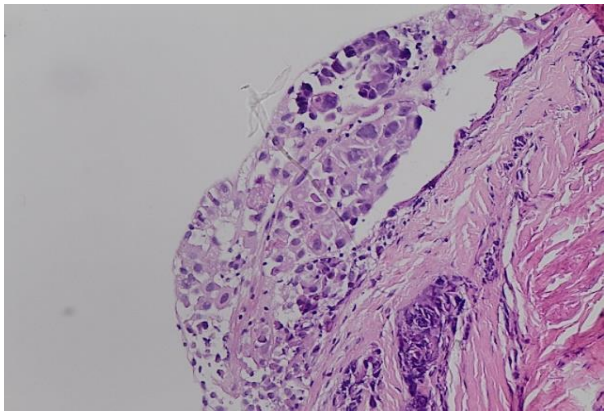

Fig. 2A. H&E

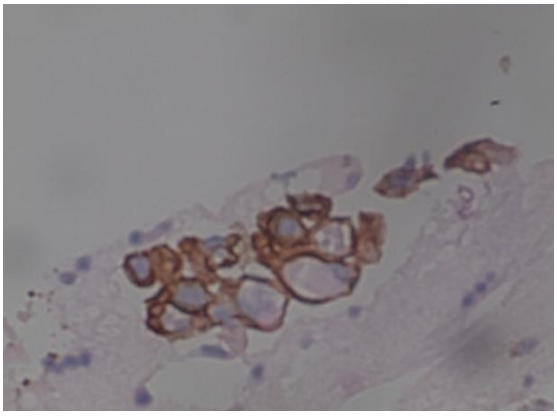

Fig. 2B. CK-7

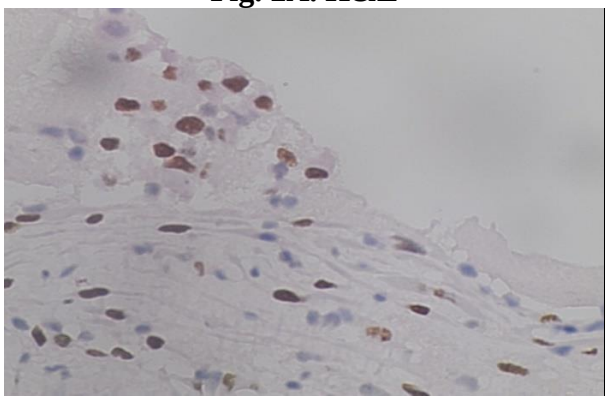

Fig. 2C.TTF-1

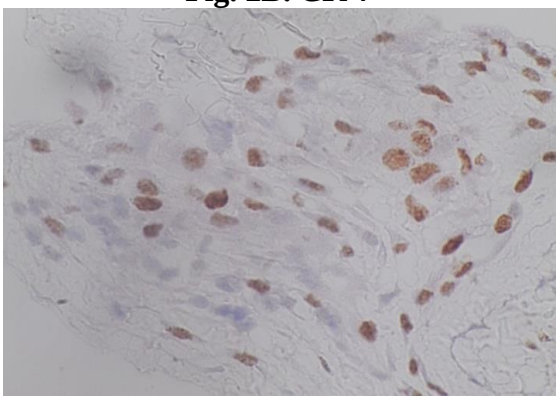

Fig. 2D. WT-1

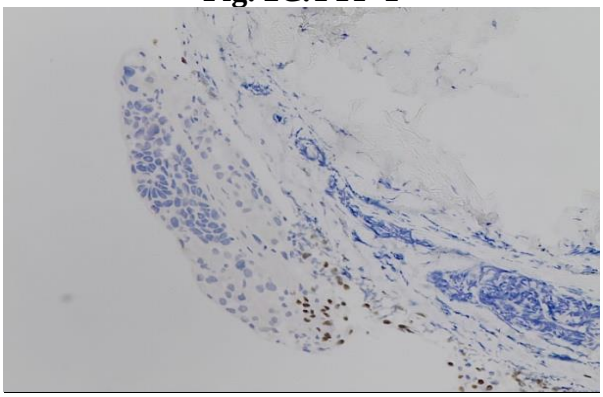

Fig. 2E. Desmin

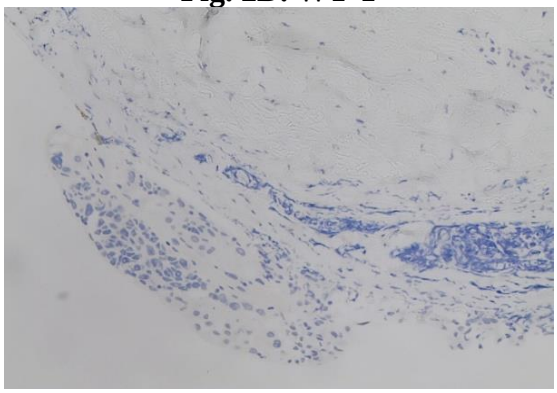

Fig. 2F. CK-20

Figure 2B-2F: H&E stained slides revealed the pleomorphic cells adhered to the underlying pleural tissue, highly suspicious of metastatic non-small cell carcinoma of left pleural with primary elsewhere (Fig.2A) (x20 magnification). IHC staining slides revealed strong positive staining for CK-7 (Fig.2B) (x40 magnification), TTF-1(Fig. 2C) (x10 magnification), Weaker stain on WT-1(Fig.2D) (x10 magnification) and Desmin (Fig.2E), but negative for CK-20 (Fig. 2F) (x10 magnification), CDX2 and P63.

References

1. Varadhachary GR and Raber MN: Carcinoma of unknown primary site. *N Engl J Med* 2014; 371:757-765 DOI: 10.1056/NEJMra1303917
2. Rajeev LK, Asati V, Lokesh KN et al Cancer of Unknown Primary: Opportunities and Challenges. *Indian J of Med and Paedtr Oncology*. 2018; 39:219-26. Online publication: 2021-06-23
3. Bochtler T and Kramer A: Does Cancer of Unknown Primary (CUP) Truly Exist a a Distinct Cancer Entity? Front. *Oncol*. 2019; 9: 1-8. https://doi.org/10.3389/fonc.2019.00402
4. Selves J, Long-Mira E, Mathieu M-C et al Immunohistochemistry for Diagnosis of Metastatic Carcinomas of Unknown Primary Site. *Cancer (Basel)*. 2018; 10(4): 108 doi: 10.3390/cancers10040108
5. Benderra M.A., Ilie M., Hofman P., Massard C. Standard of care of carcinomas on cancer of unknown primary site in 2016. *Bull. Cancer*. 2016; 103:697–705. doi:10.1016/ j.bulcan. 2016.05.003.
6. Bayrak R., Haltas H., Yenidunya S. The value of CDX2 and cytokeratins 7 and 20 expression in differentiating colorectal adenocarcinomas from extraintestinal gastrointestinal adenocarcinomas: Cytokeratin 7−/20+ phenotype is more specific than CDX2 antibody. *Diagn. Pathol*. 2012; 7:9. doi: 10.1186/1746-1596-7-9.
7. Salari K, Spulak ME, Cuff J, et al. CDX2 is an amplified lineage-survival oncogene in colorectal cancer. *Proc. Natl. Acad. Sci. USA.* 2012;109: E3196–E3205. doi: 10.1073/pnas.1206004109.
8. Olsen J, Eiholm S, Kirkeby LT, et al. CDX2 downregulation is associated with poor differentiation and MMR deficiency in colon cancer. *Exp. Mol. Pathol.* 2016. 100:59-66. doi: 10.1016/j.yexmp.2015.11.009.
9. Wang HL, Kim CJ, Koo J, et al. Practical immunohistochemistry in neoplastic pathology of the gastrointestinal tract, liver, biliary tract, and pancreas. *Arch. Pathol. Lab. Med.* 2017; 141:1155–1180. doi: 10.5858/arpa.2016-0489-RA.
10. Ji YPark, Seung HJ, Hwan IKim, et.al. Thyroid transcription factor (TTF)-1 expression is a diagnostic marker and a good prognostic indicator for lung adenocarcinoma patients with and without EGFR-sensitizing mutations. *BMC Cancer* 2019, 19:574. https://doi.org/10.1186/s12885-019-5792-0
11. Sun A Kim & Markku Miettinen. Aberrant Expression of Desmin in Primary Lung Cancer is observed exclusively in Carcinomas with Neuroendocrine Differentiation. *Am J Clin Pathol* 2018, 149 (suppl_1): S15-S16.DOI: 10.1093/ajcp/aqx116.034
12. Keiko N, Takashi K, Eroko Matsuda et.al. Immunohistochemical analysis of WT1 antigen expression in various solid cancer cells. *Anticancer research*. 2016, 36: 3715-3724.
13. Chapel DB, Schulte JJ, Husain AN, and Krausz T. Application of immunohisto-chemistry in diagnosis and management of malignant mesothelioma. *Transl Lung Cancer Res*. 2020, 9(Suppl 1): S3-S27. DOI: 10.21037/tlcr.2019.11.29.
14. Zhang K, Deng H and Cagle PT. Utility of immunohistochemistry in the diagnosis of pleuropulmonary and mediastinal cancers: A Review and Update. *Arch Pathol Lab Med.* 2014; 138 (12): 1611-1628.
15. Selves J, Long-Mira E, Mathieu M-C, Rochaix P, and Ilie M. Immunohistochemistry

for diagnosis of metastatic carcinomas of unknown primary site. *Cancers (Basel).* 2018; 10 (4): 108. DOI: 10.3390/cancers10040108
16. Conde E, Angulo B, Redondo P, et.al. The use of P63 Immuno-histochemistry for the identification of squamous cell carcinoma of the lung. *PLoS ONE 5*(8): e12209. doi:10.1371/journal.pone. 0012209 August 2010; 5 (8): e12209
17. Pelosi G, Fabbri A, Tamborini, E, et al. Challenging Lung Carcinoma with Coexistent ΔNp63/p40 and Thyroid Transcription Factor-1 labeling within the same individual tumor Cells. *J. Thorac. Oncol*. 2015; 10, 1500–1502.
18. Hayashi, T.; Takamochi, K.; Yanai, Y.; Mitani, M.; Tomita, H.; Mogushi, K.; Suehara, Y.; Takahashi, F.; Suzuki, K.; Saito, T.; et al. Non small cell lung carcinoma with diffuse co-expression of thyroid transcription factor-1 and ΔNp63/p40. *Hum. Pathol*. 2018; 78, 177–181
19. Cabibi D, Bellavia S, Giannone AG et al. TTF-1/p63-Positive Poorly Differentiated NSCLC: A histogenetic hypothesis from the basal reserve cell of the terminal respiratory unit. *Diagnostics.* 2020; 10, 25, 1-9 https://doi.org/10.3390/diagnostics10010025
20. Wang J-Y, Wang X-m, Xu X-y, et al. Expression and significance of CK5/6, P63, P40, CK7, TTF-1, NapsinA, CD56, Syn and CgA in biopsy specimen of Squamous Cell Carcinoma, Adenocarcinoma and Small Cell Lung Carcinoma. *Int. J. Morphol*. 2020; 38 (2): 247-251.
21. Steurer S, Riemann C, Büscheck F, et al. p63 expression in human tumors and normal tissues: a tissue microarray study on 10,200 tumors. *Biomarker Research*. 2021; 9 (7): 1-14. https://doi.org/10.1186/s40364-021-00260-5