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Case Series

Pathology Section

Cytological Diagnosis of Malignant Pleural Effusion caused by Metastatic Squamous Cell Carcinoma: A Series of Four Cases

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ABSTRACT

The majority of malignant pleural effusions are caused by adenocarcinomas, with the most common primary sites being the lung and breast in men and women, respectively. Metastatic squamous cell carcinoma in serous effusions is rare, accounting for less than 3% of all malignant effusions. The most common primary site of origin for metastatic squamous cell carcinoma involving serous effusions is the lung, followed by the head and neck, oesophagus, and cervix. Well-differentiated squamous cell carcinoma in pleural effusion, characterised by keratinised cells with hyperchromatic nuclei, tadpole cells, and fiber cells, is exceedingly rare. Poorly differentiated squamous cell carcinomas often present a diagnostic challenge and can be mistaken for poorly differentiated adenocarcinoma, malignant mesothelioma, or reactive mesothelial hyperplasia. Immunohistochemistry is often required for a definitive diagnosis. Making an accurate diagnosis is crucial for providing optimal treatment to the patient. In this series, four cases (56 years old male,69 years old male, 60 years old female and 81 years old male) of malignant pleural effusion caused by metastatic squamous cell carcinoma arising from the lung, oropharynx, cervix, and oesophagus were examined. While one of the cases involved a well-differentiated squamous cell carcinoma with characteristic cellular morphology that allowed for a straightforward diagnosis, the other three cases were poorly differentiated squamous cell carcinomas that required cell block preparation and immunohistochemistry for confirmation.

Keywords: Immunohistochemistry, Keratinized cells, Neoplasm metastasis

INTRODUCTION

Malignant effusions are most often caused by metastatic adenocarcinoma. Serous effusions due to metastatic squamous cell carcinoma are rare, accounting for only 0.5-2.7% of all malignant effusions [1]. Well-differentiated squamous cell carcinoma cells exhibit characteristic cytologic features, enabling a reliable morphological diagnosis. Poorly differentiated squamous cell carcinoma in effusions, due to its rarity and lack of cytomorphological differentiation, may be misdiagnosed as poorly differentiated adenocarcinoma or sometimes as malignant mesothelioma [2]. Squamous cell carcinoma, in comparison to adenocarcinoma, has a poorer prognosis. It has a lower diagnostic yield in pleural fluid cytology as its cells are shed less into effusions due to their tight intercellular junctions and robust anchors to the basement membrane [3].

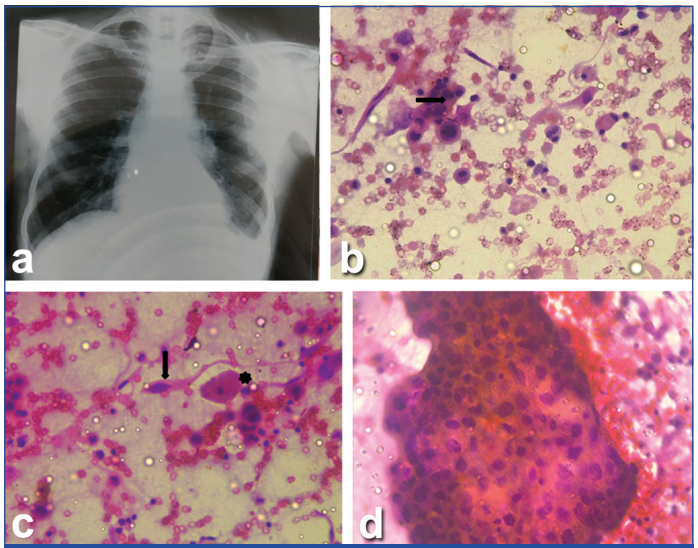
This study describes four cases of malignant pleural effusion caused by metastatic squamous cell carcinoma. Two cases had no prior history of malignancy, and pleural effusion was the initial manifestation. The diagnosis of squamous cell carcinoma was made from pleural fluid cytology smears. Radiological investigations revealed a primary lung malignancy. Two patients with a history of squamous cell carcinoma of the cervix and oropharynx, respectively, were treated with chemoradiation and later presented with pleural effusion.

Case 1

A 56-year-old male patient presented with complaints of cough and dyspnoea lasting for two weeks. The patient was a smoker and had no history of tuberculosis or any other significant past medical conditions. Upon examination, the patient was afebrile, with a pulse rate of 90/min and a respiratory rate of 26/min. Dullness on percussion and decreased breath sounds were observed in the left 6th, 7th, and 8th intercostal spaces. A chest X-ray [Table/Fig-1a] revealed a left hilar mass and left-sided pleural effusion. The provisional diagnosis was lung carcinoma with malignant pleural effusion, with a differential diagnosis of TB lung with effusion. Pleural tapping was performed, and 5 mL of red-coloured fluid was sent for cytological study.

The pleural fluid cytology smear showed dispersed cells, both singly and in occasional clusters. The cells exhibited moderate to abundant dense eosinophilic to orangeophilic cytoplasm, well-defined cell borders, and pleomorphic hyperchromatic nuclei. Fiber cells and tadpole cells were also observed [Table/Fig-1b-d].

A diagnosis of well-differentiated squamous cell carcinoma in pleural effusion was made. The final diagnosis was primary lung squamous cell carcinoma with metastasis to the pleural cavity. Unfortunately, the patient passed away after one cycle of chemotherapy.

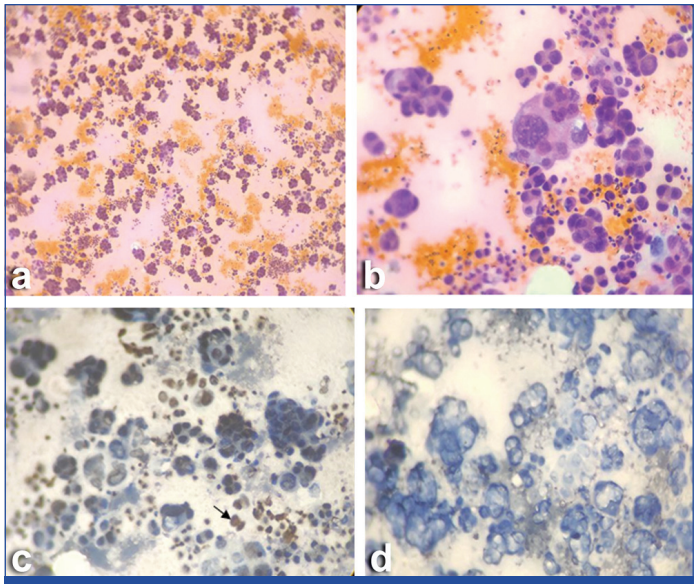


[Table/Fig-1]: a) Chest X-ray showing a left hilar mass lesion; b) Cytology smear showing fiber cells (indicated by arrow, pap stain x400); c) tadpole cell indicated by arrow, keratinised cells with pyknotic nuclei indicated by asterisk (pap stain x 400); d) large cluster of cells with orangeophilic cytoplasm and pleomorphic hyperchromatic nuclei (pap stain x400).

Case 2

A 69-year-old male patient presented with a cough, dyspnoea, and right-sided pleuritic chest pain lasting for three weeks. He was a non-smoker and non-alcoholic. The patient had a past history of oropharyngeal squamous cell carcinoma, for which he underwent radiotherapy one year ago. Upon examination, his vitals were stable, and breath sounds were diminished on the right-side of the chest. A chest X-ray revealed right-sided pleural effusion. A Computerised Tomography scan of the thorax showed a soft tissue density nodule with spiculated borders, measuring 15.3×15 mm in the apex of the right lung. The provisional diagnosis was lung and pleural metastasis from primary oropharyngeal squamous cell carcinoma, with a differential diagnosis of primary lung carcinoma with metastasis to the pleural cavity. A 5 mL red-coloured pleural fluid sample was sent for cytological study.

The pleural fluid cytology smears showed cells arranged in spherical clusters and dispersed singly [Table/Fig-2a]. The cells exhibited a moderate amount of cytoplasm, a high nuclear to cytoplasmic ratio, pleomorphic hyperchromatic nuclei with coarsely granular chromatin [Table/Fig-2b]. Occasional bizarre cells were observed. A cytological diagnosis of poorly differentiated carcinoma was made. Immunohistochemistry study was conducted on the cytology smears, revealing strong nuclear positivity for p63 [Table/Fig-2c], which confirmed their squamous origin, and Thyroid Transcription Factor (TTF-1 negativity [Table/Fig-2d], which ruled out the possibility of a non-squamous lung carcinoma.



[Table/Fig-2]: a) Cytology smear showing cells arranged in small clusters and singly (pap stain x100); b) Large pleomorphic cells with hyperchromatic nuclei are seen (pap stain x400); c) Neoplastic cells show nuclear positivity for p63 (indicated by arrow, x400); d) Neoplastic cells are negative for TTF-1(x400).

A diagnosis of poorly differentiated squamous cell carcinoma in pleural effusion was made. The final diagnosis was primary oropharyngeal squamous cell carcinoma with metastasis to the lung and pleural cavity. The patient is currently undergoing chemotherapy.

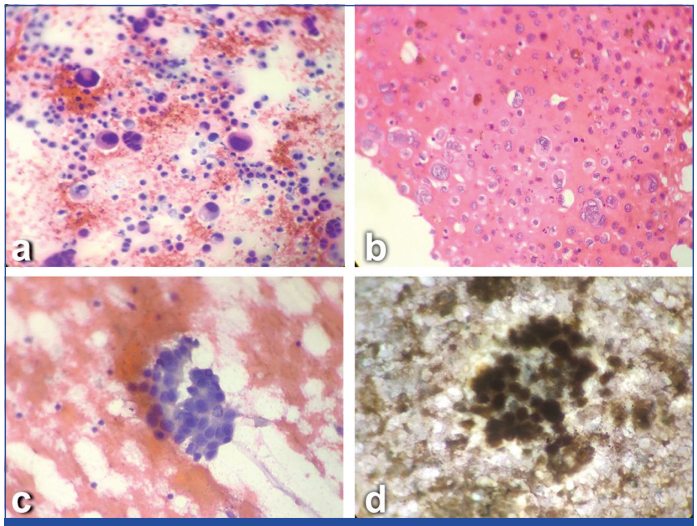
Case 3

A 60-year-old female patient presented with breathlessness lasting for two weeks. She had a history of squamous cell carcinoma of the cervix, for which she underwent chemoradiation one year ago. Upon examination, she was afebrile, had tachypnea (respiratory rate-32/min), diminished breath sounds on the left-side of the chest, and an enlarged, single, hard left supraclavicular lymph node measuring 2×2 cm. A chest X-ray revealed a left-sided massive pleural effusion. One litre of red-coloured pleural fluid was sent for cytological study.

The pleural fluid cytology showed a cellular smear with cells dispersed singly and arranged in small clusters [Table/Fig-3a]. The cells had sharp cell borders, moderate to abundant cytoplasm, and pleomorphic hyperchromatic nuclei. Bizarre cells and multinucleated tumour cells were observed. Mesothelial cells were also seen in a background of blood.

The cell block preparation exhibited cells dispersed singly, with a moderate amount of cytoplasm and nuclei displaying irregular contours and coarse granular chromatin [Table/Fig-3b].

The fine needle aspiration cytology smears of the left supraclavicular lymph node showed atypical cells in clusters. These cells had a moderate amount of dense eosinophilic cytoplasm and pleomorphic hyperchromatic nuclei [Table/Fig-3c]. The background displayed lymphocytes and blood. A cytological diagnosis of metastatic poorly differentiated carcinoma, possibly of squamous origin, was made for the pleural fluid and lymph node aspirate smears. Immunohistochemistry using p63 was performed on the lymph node aspirate smear, revealing diffuse strong nuclear positivity [Table/Fig-3d], confirming squamous differentiation.



[Table/Fig-3]: a) Pleural fluid cytology smear showssingly dispersed pleomorphic cells with hyperchromatic nuclei (pap stain x400); b) Cell block preparation of pleural fluid shows dispersed cells with marked nuclear atypia (H&E stain x400); c) Left supraclavicular lymph node FNAC smear shows a cluster of atypical cells (pap stain x400) d) Neoplastic cells show strong nuclear positivity for p63 on lymph node aspirate smears (x400).

The final diagnosis was primary squamous cell carcinoma of the cervix with metastasis to the pleural cavity and supraclavicular lymph node. Unfortunately, the patient passed away one week after initiation chemotherapy.

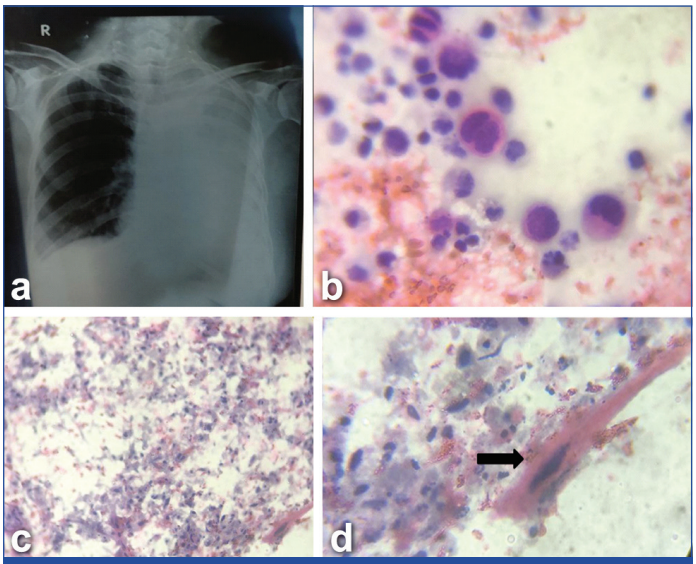
Case 4

An 81-year-old female patient presented with dysphagia and weight loss lasting for one month, and dyspnoea lasting for two weeks. Upon examination, she appeared emaciated, had tachypnea (respiratory rate-34/min), and an 8×8 cm hard swelling over the sternum. Diminished breath sounds were observed on the left-side of the chest. A chest X-ray revealed a left-sided massive pleural effusion [Table/Fig-4a]. Endoscopic examination revealed an ulceroproliferative growth measuring 5 cm in the distal 7 cm of the oesophagus. Yellow-coloured pleural fluid, with a volume of one litre, was sent for cytological study.

The pleural fluid cytology smear showed cells dispersed singly and arranged in small clusters. The cells had a moderate to abundant cytoplasm, well-defined cell borders, and pleomorphic hyperchromatic nuclei [Table/Fig-4b]. The background displayed mesothelial cells.

Fine Needle Aspiration Cytology (FNAC) of the sternal swelling was performed. The smears showed cells dispersed singly, with a moderate amount of dense eosinophilic to orangeophilic cytoplasm and hyperchromatic pyknotic nuclei [Table/Fig-4c,d]. The background showed necrotic debris. The oesophageal biopsy revealed a poorly differentiated squamous cell carcinoma.

The final diagnosis was squamous cell carcinoma of the oesophagus with metastasis to the sternum and pleural cavity. All cases have been summarised in [Table/Fig-5].



[Table/Fig-4]: a) Chest X-ray PA view shows left-sided massive pleural effusion; b) Pleural fluid cytology smear shows singly dispersed pleomorphic cells with hyperchromatic nuclei (pap stain x400); c) FNAC smear from sternal swelling shows cells in a necrotic background (pap stain x100); d) FNAC smear from sternal swelling-cell showing squamous differentiation (indicated by arrow) (pap stain x400).

S. No.	Age	Sex	Effusion cytology diagnosis	Primary site of malignancy	Secondary sites
1	56	M	Well differentiated squamous cell carcinoma	Lung	Pleural cavity
2	69	M	Poorly differentiated squamous cell carcinoma	Oropharynx	Lung, pleural cavity
3	60	F	Poorly differentiated squamous cell carcinoma	Cervix	Lymphnode, pleural cavity
4	81	F	Poorly differentiated squamous cell carcinoma	Oesophagus	Sternum, pleural cavity

[Table/Fig-5]: Shows age and sex of patients, cytological diagnosis, primary site of malignancy and secondary site of metastasis.

DISCUSSION

Serous fluid cytology is an essential diagnostic test for detection and categorising malignancies based on their morphological characteristics. Metastatic adenocarcinoma accounts for the majority of malignant effusions in adults. Although squamous cell carcinoma is a common malignancy, it is rarely encountered in serous effusions. The pleural cavity is the most commonly involved body cavity, followed by the peritoneal and pericardial cavities [1]. The lung, larynx, and cervix are the most common primary sites for squamous cell carcinoma metastasising to body cavities [2]. In this case series, the primary sites of squamous cell carcinoma metastasising to the pleural cavity were the lung, oropharynx, cervix, and oesophagus.

The largest published series includes a study of 46 cases of metastatic squamous cell carcinoma collected from 9,297 effusions over a span of 33 years. Squamous cell carcinoma of the lung was the most common origin in the study, accounting for 13 out of 34 pleural fluid samples, 2 out of 4 pericardial fluid samples, and 1 out of 8 peritoneal samples. Other primary sites included the female genital tract and larynx [3].

In another study of 277 cases of non-small cell lung carcinoma with malignant pleural effusion, 29 were squamous cell carcinomas and 248 were adenocarcinomas. Pleural fluid cytology had a low diagnostic yield in cases of squamous cell carcinoma with malignant effusion, and these patients had reduced survival compared to those with adenocarcinoma [4]. Squamous cell carcinoma cells have tight intercellular junctions and are firmly anchored to the basement membrane, resulting in reduced shedding of squamous cells in effusions compared to adenocarcinomas [5].

The diagnosis is straightforward when serous effusions are involved in metastatic, well-differentiated squamous cell carcinoma. It typically exhibits a predominantly single-cell pattern with occasional small clusters. The cells have well-defined cell borders, dense eosinophilic to orangeophilic cytoplasm, and pleomorphic hyperchromatic nuclei. Tadpole cells, fiber cells, anucleated cells, keratinous debris, and squamous pearls may also be observed [1]. Serous effusions involved in other malignancies may show small degenerated/necrotic orangeophilic tumour cells that mimic keratinising cells of squamous cell carcinoma [6].

Making a diagnosis of poorly differentiated squamous cell carcinoma in serous effusions is challenging as its cytological features overlap with those of poorly differentiated adenocarcinoma, malignant mesothelioma, and reactive mesothelial hyperplasia [7]. However, certain features such as a single-cell presentation, the presence of many bizarre nuclear forms, coarse chromatin, and cells with sharp cytoplasmic outlines can indicate a squamous cell carcinoma, especially in the context of a known clinical history of a primary squamous cell carcinoma [1]. It is crucial to make an accurate diagnosis as squamous cell carcinoma requires a different treatment protocol compared to adenocarcinomas. Immunohistochemistry can aid in confirming the diagnosis. Squamous cell carcinoma cells will test positive for p63, p40, and Cytokeratin5/6 [8].

Metastatic adenocarcinoma reacts positively to Carcinoembryonic Antigen (CEA), Ber-EP4, and MOC-31 [9]. Thyroid transcription factor-1 and Napsin A have high specificity for lung adenocarcinomas [4]. Malignant mesothelioma cells will show positivity for mesothelial markers (Wilm's tumour gene 1, calretinin) and Epithelial Membrane Antigen (EMA), while reactive mesothelial cells will show positivity for mesothelial markers (WT 1, calretinin) and desmin [10]. Published literature suggests that the pleural cavity is the most commonly involved secondary cavity [Table/Fig-6] [4,11-16].

S. No.	Authors	No. of SCC cases with malignant effusion	Body cavity involved	Primary sites of SCC
1	Dorry M et al., [4], 2021	29	Pleural cavity	Lung
2	Llanos N and Vera Roman JM [11], 1999	1	Pleural cavity	Urinary bladder
3	Joglekar K et al., [12], 2016	1	Pleural cavity	Skin
4	Paul P et al., [13], 2023	1	Pleural cavity	Oral cavity
5	Ishikawa H et al., [14], 1999	1	Pleural cavity	Gingiva
6	Gamez RG et al., [15], 2009	1	Pleural cavity	Cervix
7	Erra S et al., [16], 2016	1	Pleural cavity	Vulva

[Table/Fig-6]: Shows primary site of squamous cell carcinoma and secondary site of metastasis in various published studies [4,11-16].

CONCLUSION(S)

Metastatic squamous cell carcinoma involving serous effusions is rare, and well-differentiated squamous cell carcinoma causing malignant pleural effusion is exceedingly rare. Morphological mimickers of poorly differentiated squamous cell carcinoma in effusions include poorly differentiated adenocarcinoma, malignant mesothelioma, and reactive mesothelial hyperplasia. It is imperative to make a definitive diagnosis of squamous cell carcinoma as it has a worse prognosis and a different management protocol compared to adenocarcinoma. The clinical history of a primary squamous cell carcinoma and/or effusion fluid showing a predominance of a single cell population, numerous bizarre nuclear forms, and cells with a sharp cytoplasmic outline should raise the possibility of metastatic squamous cell carcinoma. Immunohistochemistry helps to confirm the diagnosis.

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