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Clinicopathological Conference Report

Pseudomesotheliomatous Adenocarcinoma of Lung: A Diagnostic Dilemma

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This case was discussed on 14th November 2012 as a staff clinicopathological exercise at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Clinical Protocol and Case Analysis: Dr Navneet Singh

CLINICAL PROTOCOL

A 52 years old farmer developed left-sided chest pain 4 months prior to admission that was dull aching, episodic, lasting for 1 to 2 minutes, relieved of its own and increased on deep inspiration. He was found to have left-sided pleural effusion. Pleural fluid analysis revealed straw colored fluid with positive stain for acid fast bacilli at Civil Hospital, Rupnagar. He was enrolled under Revised National Tuberculosis Control Programme (RNTCP) for directly observed antitubercular treatment (DOTS) as a new case. Despite 2 months of treatment, there was no symptomatic improvement and repeat evaluation showed a persistent large pleural effusion. Therapeutic thoracocentesis (2-3 times) was done followed by intercostal chest tube insertion 2 months prior to admission with drainage of approximately 200 to 300 ml of hemorrhagic fluid per day. Over a period of 2 weeks preceding admission, severity of chest pain gradually increased. Six days prior to admission, he developed high grade fever associated with rigors and chills. Breathlessness started 4 days prior to admission, was acute in onset, progressing during this time period to being present at rest and not associated with orthopnea or wheeze. There was no history of cough, expectoration, hemoptysis, swelling of feet, decreased urine output or altered sensorium. There was no significant illness in the past. He was a nonsmoker with no addictions.

On initial evaluation, he was conscious and oriented. He had tachycardia (130/min), normal blood pressure (130/70 mm Hg) and tachypnea (40/min) with use of accessory muscles of respiration. Pallor, bilateral pitting pedal edema and small right supraclavicular lymph nodes were noted. Examination of the chest revealed presence of a chest tube, reduced chest wall movements with signs of volume loss on the left side, dull note on percussion with reduced intensity of breath sounds in the left infraclavicular and left mammary areas. The clinical findings were consistent with those of pleural effusion. Per abdomen, the liver was palpable 2 cm below right subcostal margin with no other specific features. Spleen was not palpable, there was no tenderness or free fluid and bowel sounds were present. Rest of the systemic examination was unremarkable.

INVESTIGATIONS

Peripheral film: Predominant normocytic, mild anisocytosis (micro- and macrocytic), mild hypochromia.

Red cell indices: MCV—93; MCH—29.9; MCHC—32.3, RDW—14.3%; ESR—12 mm/hour.

Coagulogram (28/08): PTI—34/14 sec, PTI—41%, PTTK—49/32 sec, fibrinogen—2.03, D-dimer +ve; (18/09): PTI—27/12 sec, PTI—52%, PTTI—31/32 sec.

(12/09) S. LDH: 1,972 U/L, uric acid: 5.6 mg/dl.

Hemolytic work up: G-6-PD intermediate, plasma Hb not raised, urine Hb 14.6 mg/dl, HBsAg negative, anti-HCV Ab negative, RA factor negative, ANA negative.

Pleural fluid analysis (28/06): TC—640, DC—P30L70, Prot—5.3 gm/dl, Sugar 96 mg/dl, ADA—26.9 U/L, Gram stain –ve, bacterial C/S—sterile, AFB smear –ve, AFB culture sterile.

Pleural fluid C/S (27/08): Pseudomonas aeruginosa, *(29/08 and 01/09)*—sterile

Pleural fluid (×3): AFB smears –ve, AFB cultures (2 LJ and 1 BACTEC/MGIT) sterile.

Sputum (×1) and endotracheal aspirate (×2): AFB smears –ve, AFB cultures (LJ) sterile.

Pleural fluid cytology: (4080/12) positive for malignant cells (adenocarcinoma);

4 samples (5432/12, 5438/12, 5469/12, 5486/12)—no malignant cells.

Date	28/08	05/09	10/09	12/09	13/09	15/09	16/09	18/09
Hemogram								
Hb (gm/dl)	6.4	8.7	8.1	7.3	7.4	8.0	7.5	6.0
TLC (per μl)	19,200	30,800	25,000	18,800	40,000	28,600	29,000	26,000
DLC	P77L18 M03E02	P90L05 M02E01	P61L24 M05E02	P77L20 M02E01	P96L04			
Plt ($\times 10^5$ per μl)	1.08	1.01	0.46	0.18	0.18	0.26	0.38	0.30
Biochemistry								
Na/K (meq/l)	134/2.7	127/3.8	145/3.8	136/3.9	136/5.3	145/4.4	142/4.8	136/4.9
Urea/creat (mg/dl)	19/0.5	40/0.44	64/0.59	63/0.57	84/0.69	91/0.77	105/0.78	111/0.86
Bil–T/D (mg/dl)	0.8	1.0	3.4	6.0/5.8	4.4/3.6		1.9	
AST/ALT (U/L)	33/23	51/31	90/30	82/31	78/25		78/15	
ALP (U/L)	152	262	780	718	741		1,152	
Prot/Alb (gm/dl)	6.0/2.6	5.7/2.6	5.1/2.1	5.1/2.0	5.3/2.1		4.6/1.8	4.7/1.8
Calcium/phos (mg/dl)	8.8/2.1	8.5/1.27	8.2/3.4	5.9/4.1	5.1/3.4		NA/4.5	7.8/4.6
Arterial blood gas								
pH	7.47	7.45	7.41	7.4	7.37	7.44	7.39	7.42
PaO_2 (mm Hg)	75.6	64.3	61.7	69.7	63.8	57.4	58.9	62.2
SaO_2 (%)	96	93.5	91.7	93.8	91.3	90.7	89.9	92
$PaCO_2$ (mm Hg)	33.1	40.1	43.8	44.4	39.8	38.2	39	34.9
HCO_3 (meq/l)	23.9	27.3	27.2	26.8	22.8	25.4	23.3	22

Blood C/S (29/08): Sterile (central and peripheral); (05/09)—MRSA (central), sterile (peripheral); (13/09)—sterile.

Blood fungal C/S: Sterile

Urinalysis: (27/08) albumin +, sugar nil, M/E 3-4 RBCs, amorphous deposits +, urine C/S—sterile; urine cytology (5789/12)—no malignant cells seen.

Stool routine: Hook worm ova present; stool C/S—sterile.

Skin biopsy (S-16409/12): Smaller blood vessels in dermis show presence of fibrin thrombi in lumina. No vasculitis seen. Impression—vasculopathy.

Skin biopsy DIF (59/12): IgG neg; IgA ++ to +++ in blood vessels (BV); IgM ++ in BV; C3 ++ to +++ band test and patchy in BV. Impression—immune complex vasculitis.

Bedside 2D ECHO (04/09): No RWMA, clot, vegetation, pericardial effusion, visual EF 55-60%; (08/09)—mod TR, mild PAH (RVSRP = RAP + 32 mm Hg); (11/09): AML prolapsed, mod MR/TR, vegetation atrial side of AML/PML; (12/09): AML tip prolapsed, no vegetation, mod MR, mild AR, mild TR; RVSP = RAP + 25 mm Hg, visual EF—55 to 60%

Ultrasound abdomen (26/08): Mild to moderate B/L pleural effusion, ascites. Focal attenuation of echotexture segment 2 of liver; (09/09)—mod hepatomegaly with heterogeneous ill-defined 3 × 2.7 cm in segment 4 evolving liver abscess.

Compression USG LL (27/08): DVT involving Lt CFV, B/L SFV and B/L popliteal veins.

Compression USG B/L UL (10/09): Lt axillary vein thrombosis.

CHEST RADIOGRAPH AND CT SCAN THORAX: (DR ANINDITA SINHA)

Initial chest radiographs showed a left-sided pleural effusion. A contrast-enhanced computed tomographic (CT) scan of the chest revealed left pleural effusion and collapse of the left lung. Nodular pleural thickening was present suggesting a malignant effusion. Chest radiographs after drainage of the pleural effusion showed a left hilar prominence with reticulonodular opacities radiating from the hilum. An increase in the reticulonodular opacities were noted in the serial chest X-rays (Fig. 1) with new reticulonodular opacities appearing in the right lung. The appearance was suggestive of a lymphangitic spread of carcinoma with a right hilar node or a mass. In addition, a wedge-shaped peripheral consolidation was noted in a later X-ray in the right costophrenic angle suggesting a segmental pulmonary infarct.

Course and management: This patient was started on low molecular weight heparin in view of bilateral lower limb DVT and broad spectrum antibiotics (piperacillin/tazobactam and vancomycin). Rifampicin and isoniazid that constituted the continuation phase of ATT were continued. Thoracoscopy could not be performed due to presence of coagulopathy and poor general condition of the patient. He was shifted to respiratory ICU in view of respiratory distress and subsequently required intubation and initiation of mechanical ventilatory support. LMW heparin was discontinued after thrombocytopenia worsened. He received blood and platelet transfusions for correction of anemia and thrombocytopenia respectively. Abdominal distension and hematuria developed sequentially and transiently during the course of his hospital stay and both resolved with conservative management. While in hospital, the patient

developed bullous skin lesions and swelling over both the upper limbs. Dermatology consultation was taken and skin biopsy was performed. Axillary vein thrombosis was detected on compression ultrasound of upper limbs. Skin lesions gradually progressed to involve both lower limbs also and became gangrenous. Repeat ECHO showed new onset mitral regurgitation. So, the patient was managed on the lines of infective endocarditis with parenteral antibiotics (imipenem and vancomycin). Gradually, he developed hypotension, reduced urine output, altered sensorium and focal seizures which were managed with inotropes, antiepileptics and amphotericin (as empiric treatment for fungal sepsis). The patient sustained a cardiac arrest on september 19th from which he could not be revived.

Unit's final diagnosis was left exudative pleural effusion, tubercular, malignant, bilateral lower limb deep venous thrombosis with left axillary vein thrombosis (paraneoplastic), sepsis with multiorgan dysfunction syndrome, new onset mitral regurgitation, infective endocarditis and possibly cutaneous vasculitis. The cause of death was attributed to severe sepsis with MODS with possibility of pulmonary thromboembolism.

CASE ANALYSIS

So, the unanswered questions in this case were: Was there tuberculosis or not? Did this patient have a malignancy or not? Did he have sepsis/infective endocarditis? Were the skin lesions consistent with those seen in cutaneous vasculitis?

Coming first to tuberculosis, we know that there was a single positive pleural fluid AFB smear report from outside but that he had several subsequent smears and cultures which were negative. Pleural fluid ADA levels were within normal limits. He did not have any clinical or radiological response to ATT which on historical grounds was of adequate dosage and adequate duration. We also know that by definition pleural tuberculosis is paucibacillary and, therefore, primary treatment failure (including drug resistance) in unilateral nonempyematous pleural tuberculosis is rare. So, I am quite skeptical about this patient ever having had tuberculosis. It is distinctly unusual for pleural tuberculosis in general to have chest pain as the most prominent symptom and even more unusual for chest pain to be persistent and progressive something that was observed in this patient.

The next possibility that one should discuss in this case is a systemic vasculitic disorder. Although there were a few suggestive clinical features accompanied by abnormalities on urinalysis and the findings on skin biopsy direct immune fluorescence, it is again unusual to have persistent/progressive chest pain and large hemorrhagic effusion. Moreover, this patient had neither diffuse alveolar hemorrhage nor cavitating pulmonary nodules/masses, the most common form of pulmonary involvement in systemic vasculitis. Also, skin biopsy did not show a perivascular inflammatory infiltrate. So, I do not feel it is likely.

Moving now to malignancy, the clinical profile was quite consistent in the form of predominant and prominent chest pain, a large exudative rapidly reaccumulating hemorrhagic pleural effusion with normal ADA levels and no response to ATT, one pleural fluid cytology sample unequivocally positive, presence of a right supraclavicular lymph node and strong association of adenocarcinoma with unprovoked venous thrombosis. However, there is no definitive clue to the primary site in either clinical or investigational profile. For deciding if the primary is in the lung or at an extra thoracic site, there was a suspicion of a left hilar lung mass/consolidation on serial chest radiographs. Adenocarcinoma remains the commonest histological type of lung cancer presenting with pleural effusion and the commonest histological type in nonsmokers. Moreover, if located peripherally, the primary lesion may not be radiologically apparent. At the same time, one needs to look for other common sites for a primary adenocarcinoma namely stomach, large intestine (colon/rectum) and pancreas. Malignant mesothelioma is also a differential diagnosis for adenocarcinoma since it can have similar clinicoradiological and cytological features. However, for a mesothelioma, the classical features are lacking namely history of asbestos exposure (its strongest known risk factor) and radiological pattern of diffuse nodular pleural thickening or contraction of hemithorax (volume loss). The intriguing question is about pleural fluid cytology where only one sample was positive and four subsequent samples were negative for malignant cells. Cytological diagnosis on pleural effusions has a sensitivity of 50.0%, specificity of 97.0%, positive predictive value of 95.7% and negative predicative value of 86.4% with false positive and false negative rates being 0.5% and 31.5% respectively. A total of 71% of false negative results are due to sampling errors. It is possible that this was related to the nature of malignancy. Infact, sensitivity of pleural fluid cytology is low for tumors like malignant mesothelioma (26% *vs* 98.4% for thoracoscopic pleural biopsy) and, in these cases, it is 'typically negative despite repeated sampling'. Diagnostic yield is also dependent upon the volume of pleural fluid sent for analysis and whether cell block was prepared or not. Regarding the association of malignancy with unprovoked venous thrombosis, cancers of pancreas, colorectal, stomach and lung are most frequently associated. Thrombotic risk in lung cancer patients is 20-fold higher than in the general population. Among lung cancer patients, adenocarcinoma as compared to nonadenocarcinoma histology has a higher

risk [hazard ratio (HR) = 5.6; (95% CI = 2.4-13.1)] for development of DVT/PTE. Similarly, higher grade of tumor is associated with higher risk (HR = 2.0; 95% CI = 1.1-3.5). Diagnosis of pulmonary thromboembolism within 3 months of diagnosis of lung cancer has been shown to be a poor prognostic factor (HR = 1.5; 95% CI = 1.1-2.0). Could this patient have had both malignancy and tuberculosis? Tuberculosis can occur prior to (scar carcinoma), concurrently with (extrapulmonary) or subsequent to (following chemotherapy) diagnosis of lung cancer. However, the crux is that there are no definitive pointers to suggest tuberculosis in this patient after from an initial pleural fluid AFB positivity which is of questionable value. So, although presence of coexistent tuberculosis is theoretically plausible and possible but, for the current patient, we do not have any convincing evidence to suggest the same.

What about infective endocarditis? This patient had high grade fever, sepsis with MODS, an immune complex deposits in blood vessels, new onset valvular regurgitation and possibility of valve leaflet vegetation (although the more sensitive transesophageal echocardiography was not possible). However, there was only a single positive blood culture (MRSA). Differentiating nonbacterial thrombotic endocarditis[1,2] from infective endocarditis is not always straightforward and, in this patient with advanced untreated cancer, I would like to consider NBTE as a strong possibility.

Dermatological involvement in this patient was suggestive of cutaneous vasculitis, since IgA, IgM and C3 deposition in/around blood vessels was seen on direct immunofluorescence. Main pathogenetic mechanisms of relevance in the index patient include sepsis (bacterial or nonbacterial), infective endocarditis and as a paraneoplastic phenomenon.[3] Cutaneous leukocytoclastic vasculitis is seen in less than 5% of patients with definite infective endocarditis. On the other hand, the most common (paraneoplastic) vasculitis seen in patients with solid tumors is cutaneous leukocytoclastic vasculitis while the other types (Henoch-Schonlein purpura, polyarteritis nodosa and giant cell arteritis) are quite rare. The commonest malignancies include carcinomas of urinary organs (40%), lung (26.7%) and GIT (26.7%). Since there is a concordance between paraneoplastic cutaneous vasculitis and tumor activity, I feel this entity should be strongly considered in our patient.

Coming next to pulmonary embolism, we know this patient had proven DVT of both lower limbs at admission and that he also developed new onset venous thrombosis in the left upper limb during hospitalization. This combined with the background of an active untreated malignancy and inadequate anticoagulation is likely to have predisposed him to pulmonary thromboembolism. This is supported by the fact that he had both new onset/worsening dyspnea and a new wedge-shaped opacity in the right lower zone on chest radiograph, the latter being suggestive of a pulmonary infarct. An important question that one needs to consider is whether it was thromboembolism or tumor embolism. Tumor embolism mimics thromboembolism clinically and although less common than the latter, it is not uncommon in the setting of advanced untreated cancer. Its presentation is typically in the form of unexplained/out of proportion dyspnea with/without pulmonary hypertension. Since this is mostly an autopsy diagnosis, it is definitely an entity that needs exclusion in this patient.

Acute worsening in this patient was characterized by high grade fever, progressive dyspnea leading to respiratory failure, marked leukocytosis, coagulopathy/DIC and two positive bacterial cultures (pseudomonas aeruginosa in pleural fluid and MRSA in blood). Thus, he had features suggestive of sepsis with MODS. Did this patient have fungal sepsis? He had predisposing factors for fungal sepsis in the form of advanced malignancy (which by itself is a state of relative immunosuppression), administration of broad spectrum antibiotics in the recent past and prolonged hospitalization/ICU stay. However, what is really not clear is that if it was indeed fungal sepsis, first what was the etiological agent (Mucor/Rhizopus species *vs* Aspergillus species *vs Candida* species) since no fungus had been demonstrated/isolated in clinical specimens from any site and second what was the focus for dissemination?

Other issues in this patient that merit discussion include hepatic dysfunction and bicytopenia. The former could be either due to development of a liver abscess which is possible in setting of sepsis. Another explanation could be liver metastases although the temporal course of events for liver involvement was too rapid than what one would expect normally. A third possibility is nonmetastatic hepatic dysfunction (something analogous to Stauffer syndrome) which has been mostly described with renal cell carcinoma and would be quite rare for lung carcinoma. Bicytopenia is possibly due to sepsis although marrow infiltration is not unusual in disseminated (stage IV) cancer. Microangiopathic hemolytic anemia either related to infective endocarditis or as a paraneoplastic phenomenon could also lead to bicytopenia. However, there were no schistocytes on peripheral blood smear.

In summary, my final diagnosis is:

- Malignant pleural effusion (stage IV)
  - Adenocarcinoma of lung (most likely)
  - Primary tumor of stomach/colon/pancreas and primary pleural malignant mesothelioma (less likely)

- Bilateral lower limb and left upper limb deep venous thrombosis
  - Pulmonary thromboembolism (likely)
  - Pulmonary tumor embolism (possibly)
- Cutaneous vasculitis
  - Likely paraneoplastic (sepsis/embolism related)
- Superadded sepsis (bacterial and/or fungal) with MODS
  - Liver abscess/bacterial/metastatic
- Endocarditis
  - Paraneoplastic (NBTE) (likely)
  - Infective endocarditis (less likely).

OPEN HOUSE DISCUSSION

- *Dr Sanjay Jain:* There is no doubt that this patient had an adenocarcinoma in the pleural fluid. The issue is whether it is from the lung or anywhere from the GIT or kidney. Another issue would be presence of severe leukocytosis, which could be secondary to presence of fever. The presence of hematuria probably indicates that this patient might have a primary in the kidney.
- *Dr V Sakhuja:* The CT scan did not show any lesions in the upper pole of the kidneys. The vasculitis present in this patient had deposition of IgA antibodies in the vessels. But, the patient had bullous lesions rather than purpuric spots, which is unusual for IgA-associated vasculitis.
- *Dr Navneet:* IgA deposition in the vessels can be seen as part of paraneoplastic syndromes.
- *Dr Sanjay Jain:* A panel of immunohistochemistry to distinguish between adenocarcinomas of different sites as well as mesothelioma on pleural fluid cytology would be needed.
- *Dr Navneet:* The markers used are CK7, CK20, napsin A for adenocarcinomas of lung and vimentin, WT1, EMA, calretinin for mesotheliomas.

PATHOLOGY DISCUSSION: PM 25012 (DR AMANJIT BAL)

Antemortem skin biopsy S-16409/12 showed fibrin thrombi in small dermal blood vessels with no evidence of vasculitis.

A complete autopsy was performed on this 52 years old male. The prosecutor noticed discoloration of both upper limbs extending up to the elbow with blisters, discoloration of both feet with edema, and discoloration of the pinna. There was an intercostal drainage tube stoma on left side of chest. Both pleural cavities contained 1L of straw-colored fluid and were obliterated by dense adhesions. The peritoneal and pericardial cavities were within normal limits. The lungs weighed 950 gm. The trachea and major bronchi were normal. The pleura over the left lung (Fig. 2A) was markedly thickened. On cut section, the left lung parenchyma was subcrepitant with prominent bronchial markings with thickened fibrous rims. Multiple small nodules measuring 0.2 cm were scattered throughout the lung parenchyma but no definite tumor nodule could be identified. The right lung showed patchy pleural thickening and on slicing small nodules of 0.2 to 0.3 cm could be identified. Both lungs show thrombi in small pulmonary vessels resulting in hemorrhagic infarcts. On microscopic examination, the left lung showed a pseudomesotheliomatous peripheral adenocarcinoma of acinar type (Fig. 2B), which was mucin producing and had spread through lymphatics to the parenchyma of both the lungs. Tumor cells were positive for CK7 (Fig. 2C) and TTF-1 (Fig. 2D) and negative for CK5/6, calretinin and WT-1. There were multiple foci of preinvasive lesions in both the lungs, i.e. atypical adenomatous hyperplasia (Fig. 3A), pulmonary thromboemboli, infarcts and pulmonary arteriopathy (Fig. 3B) with medial hypertrophy. Evidence of terminal bronchopneumonia was also seen. The liver (Fig. 3C) weighed 1,600 gm and, on cut section, 1 cm sized nodules were seen in both lobes and were coalescing to form a large nodule of 5 cm with central hemorrhage in the left lobe. No thrombus was seen in the portal vein. Microscopy revealed metastatic adenocarcinoma (Fig. 3D). Both adrenals (Fig. 4A), spleen (Fig. 4B), lymph nodes (Fig. 4C) (hilar, carinal paratracheal, mesenteric and peripancreatic), appendix, bone marrow and kidneys (intraglomerular, Fig. 4D) showed metastatic adenocarcinoma. The heart weighed 250 gm and there was a thrombus in the right auricle along with vegetations (Fig. 5A) on atrial surface of mitral valve (0.5 × 0.5 cm) and on the free edge of aortic valve (0.8 cm). The underlying valves were normal. Microscopy revealed a nonbacterial thrombotic endocarditis (Fig. 5B) with absence of any

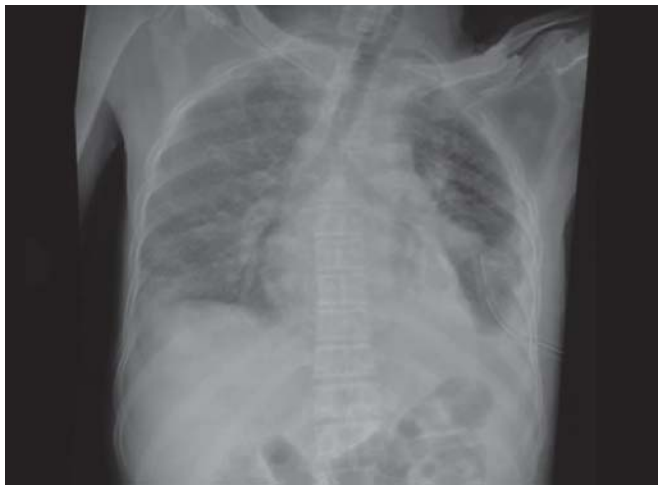


Fig. 1: Chest X-ray shows reticulonodular opacities in B/L lung fields with a left pleural effusion and a left hilar prominence suggestive of a mass. A wedge-shaped consolidation infarct is seen in the right costophrenic angle

organism. The spleen weighed 110 gm and cut section revealed wedge-shaped hemorrhagic infarcts (Fig. 5D) and multiple small nodules of metastatic adenocarcinoma. Both the kidneys showed wedge-shaped infarcts (Fig. 5C) with thrombi in the interlobar and arcuate arteries along with intraglomerular metastasis (see Fig. 4D). The brain weighed 1,280 gm. There was asymmetry of the cerebral hemispheres with a left-sided swelling, marked uncal and tonsillar herniation and subarachnoid hemorrhage in frontoparietal region. Coronal slices showed areas of softening from anterior to posterior in the middle cerebral artery (MCA) territory and hemorrhages in internal capsule at level of anterior commissure. Superior sagittal sinus, cerebellum and brainstem were grossly normal. On microscopy, there was a thrombus in the MCA with the resultant infarct. The inferior vena cava, left common iliac vein, inferior thyroid vein showed thrombi occluding their lumen. The GIT and pancreas were within normal limits.

FINAL AUTOPSY DIAGNOSIS (PM-25012): 52 YEARS MALE

- Peripheral adenocarcinoma left lung with lymphangitic carcinomatous spread to both lungs and metastases to hilar, carinal, paratracheal, mesenteric and peripancreatic lymph nodes, liver, spleen, appendix, adrenals, intraglomerular capillaries, and bone marrow.
- Extensive manifestation of a hypercoagulable state: Venous thrombosis, nonbacterial thrombotic endocarditis with embolic infarcts in spleen, kidneys and brain (left MCA territory) and pulmonary thromboembolism.
- Extramedullary hematopoiesis: Liver, spleen and adrenals.
- Terminal bronchopneumonia.

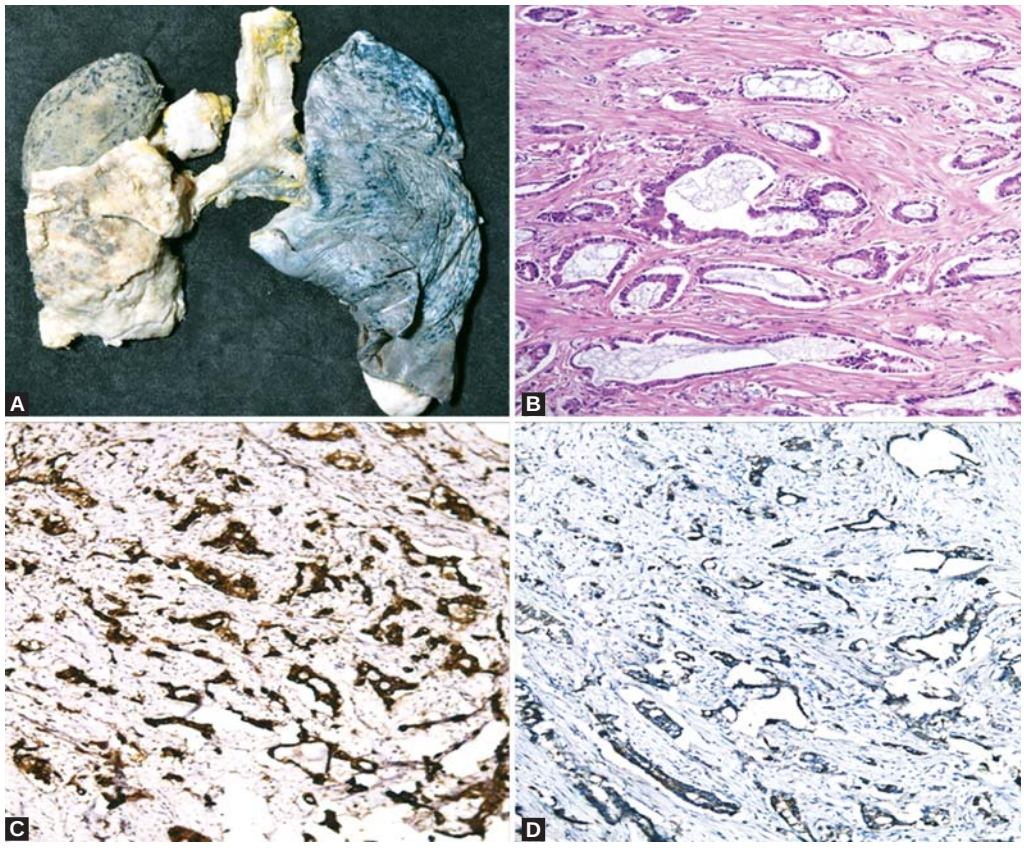
OPEN HOUSE DISCUSSION

- *Dr V Sakhuja:* We seem to have a fairly good clinicopathological correlation in this case.
- *Dr S Jain:* In cutaneous vasculitis deposition of IgM and C3 will be present as compared to IgG. IgM was absent in this case surprisingly. This otherwise supports the diagnosis of vasculitis associated with adenocarcinoma. What were the histopathology findings of the skin at postmortem?
- *Dr V Sakhuja:* The patient had history of focal seizures preterminally which were due to the cerebral infarction seen at autopsy.
- *Dr Amanjit:* Unfortunately, the involved area of the skin was not sampled. We could revise the antemortem diagnosis of skin biopsy as it was just a thrombus within the vessel wall without any evidence of vasculitis.
- *Dr Sanjay Jain:* Venous thrombosis in unusual site (axillary vein) and thrombosis refractory to therapy are possible indicators of an underlying malignancy. Since this is a disseminated malignancy, it would be possible to detect the circulating tumor cells.
- *Dr Navneet:* There are studies to detect circulating tumor cells as well as EGFR mutations in them which have been published.
- *Dr V Sakhuja:* A CT scan at a later date would have picked up a lot more lesions than the one done earlier.
- *Dr Navneet:* An unusual finding in this case was a lesion in the liver which was atypical of an abscess and was probably tumor metastasis with extensive necrosis.

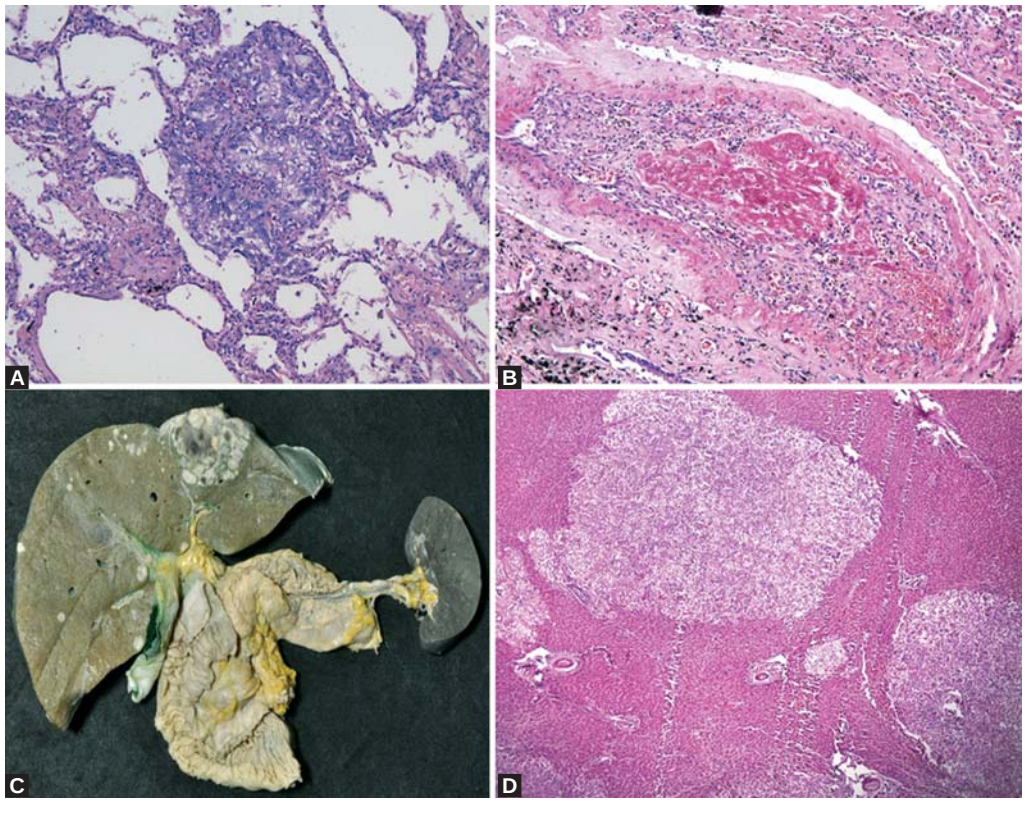
COMMENTARY

Pseudomesotheliomatous adenocarcinoma[4,5] is an uncommon variant of peripheral adenocarcinoma first described by Harwood et al in 1976. He termed this as pseudomesotheliomatous carcinoma, arising from an inconspicuous subpleural mass, generally an adenocarcinoma. It usually presents with signs of pleural thickening. Occasionally, involvement appears as a localized neoplastic growth adjacent to the parenchymal lesion and, rarely, it may spread widely over the pleura without causing effusion and simulating a malignant mesothelioma. Such spread of carcinoma lung with clinical, radiological and gross appearance mimicking a diffuse malignant pleural mesothelioma is termed as a pseudomesothelioma. The exact incidence of pseudomesothelioma is not known as the literature is limited to case reports. The differentiation between mesothelioma and pseudomesothelioma requires histological examination and demonstration of the primary lung cancer.

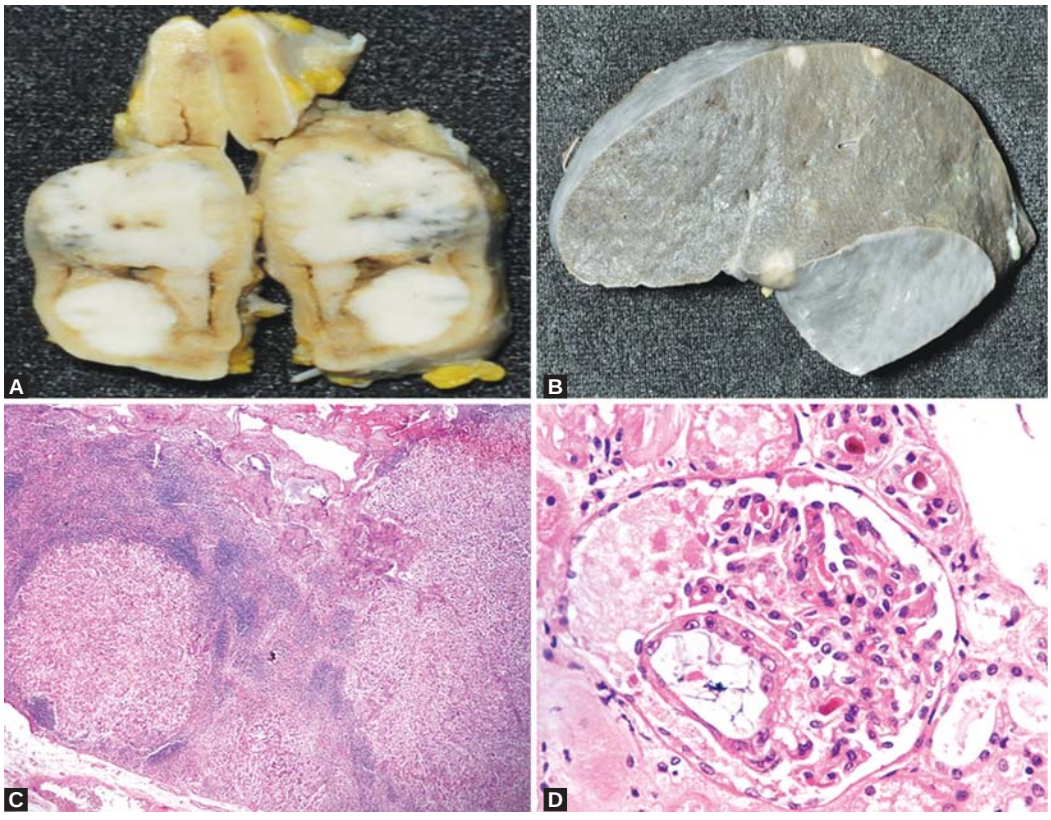
Since the first description of the association between deep vein thrombosis and pancreatic malignancy by Trousseau in 1865, many studies have confirmed the abnormally activated hemostatic system in cancer patients.[6,7] There is a 3-fold increased risk of venous thrombosis for patients with an adenocarcinoma compared to patients with a squamous cell carcinoma. DIC, a common hematologic abnormality in patients with cancer, may complicate the clinical picture any time during the course of the malignancy either when the malignancy is still occult or when it is widely disseminated as in the present case. Several factors may contribute to venous thrombosis in cancer patients, such as immobilization, surgery, procoagulant factors produced by the tumor cells, endothelial damage caused by chemotherapy or stimulation of endothelial cells to produce procoagulant material. Recent research has shown that mucins produced by carcinoma can activate platelets and generate microthrombi in mice, most likely through interaction with



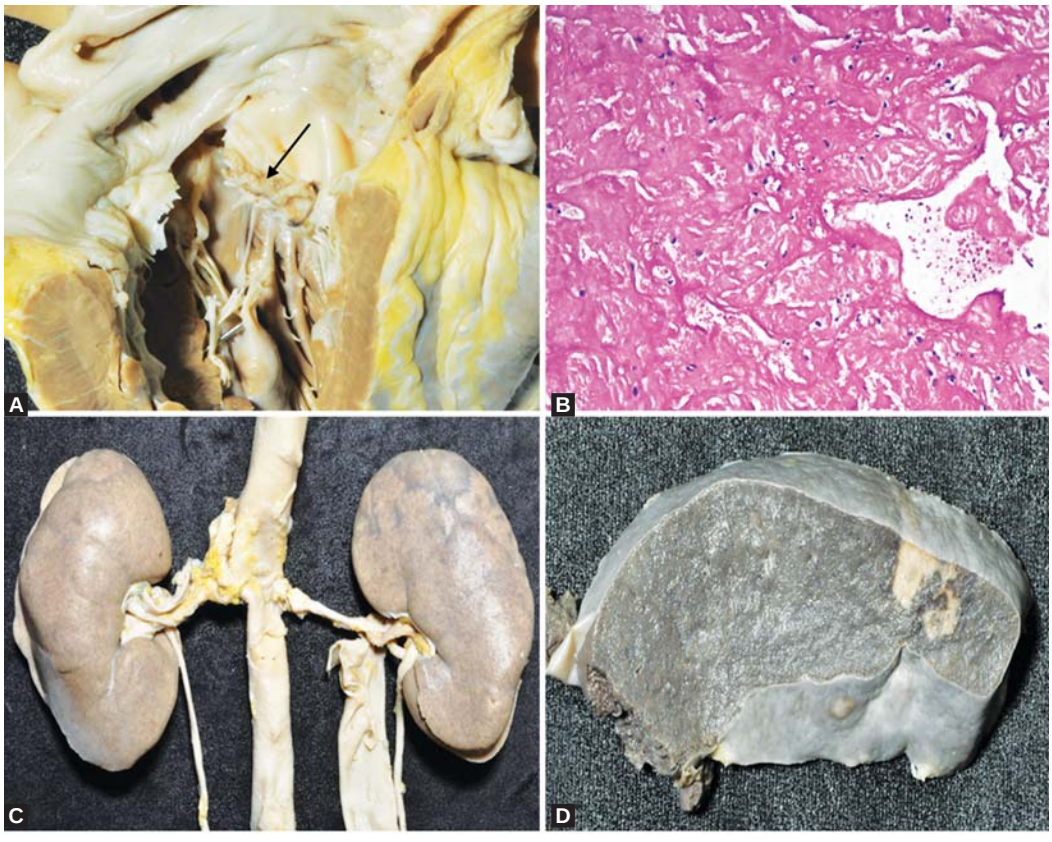
Figs 2A to D: (A) Gross photograph of lungs showing markedly thickened pleura encasing the lower lobe of left lung, (B) tumor cells arranged in the form of glands filled with mucin H&E × 200, C&D—tumor cells showing diffuse cytoplasmic positivity for CK-7, (C) nuclear positivity for TTF-1, (D) IHC × 200



Figs 3A to D: (A) Adjacent lung parenchyma showing foci of atypical adenomatous hyperplasia (200x), (B) microphotograph of pulmonary artery showing large organized thrombus (200×), (C) liver showing multiple tumor nodules which are coalescing at places with central area of hemorrhage, (D) microscopic examination of liver showing metastatic deposits of adenocarcinoma (100×)



Figs 4A to D: (A) Adrenal glands showing tumor nodules measuring 2 cm in diameter, (B) spleen showing multiple small tumor nodules measuring 1.5 cm in diameter, (C) hilar lymph node showing metastatic deposits of adenocarcinoma (200×), (D) microphotograph of kidney showing intraglomerular metastasis (400×)



Figs 5A to D: (A) Heart showing friable vegetations on atrial surface of mitral valve measuring 0.5 cm, (B) microphotograph of vegetation showing meshwork of fibrin and platelets. No bacteria or fungi were seen H&E ×200, (C) kidneys showing wedge-shaped infarcts in the upper poles, (D) spleen showing wedge-shaped infarcts

leukocyte L-selectin and platelet P-selectin because this pathology was markedly diminished in P- or L-selectin deficient mice.

Why the cardiac valves, particularly the mitral valve, should become a focus for vegetations and emboli in malignancy is obscure. A syndrome of nonbacterial verrucous endocarditis, frequent and recurrent thrombophlebitis, cerebral and pulmonary emboli associated with mucus-producing carcinomas has been described in the literature.

A paraneoplastic process should always be kept in mind in DVT of unknown etiology, although there have been no standard or pathognomonic laboratory tests for malignancy-related DIC. These patients usually have highly elevated FDP and D-dimers, indicating that a widespread clotting process has occurred and the fibrinolysis is active. The thromboembolic events could sometimes be the first clinical manifestation of paraneoplastic syndromes. The possibility of an occult malignancy should be considered while evaluating a patient with sudden onset of DVT, heart murmurs and NBTE without other obvious predisposing conditions.

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