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Case Report

Malignant Pleural Effusion – An enigma!

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1. Abstract

We report a case of 45 years old lady who presented with respiratory symptoms of breathlessness and chest pain of 15 days duration. On evaluation, she was found to have left sided exudative pleural effusion with lymphocytosis and low ADA level. Malignant cells were not found in the pleural fluid on 3 occasions. She was put on anti-tubercular treatment elsewhere on the presumptive diagnosis of tubercular effusion. However, her serum LDH: pleural fluid ADA ratio was >20 which pointed to the possibility of malignant effusion. Further computed tomography of abdomen showed diffuse thickening of the colon up to the sigmoid colon with fistulous tract between the spleen and splenic flexure of the colon with sub-capsular collection in the spleen. Multiple air fluid levels were found with collection below the left dome of the diaphragm. This raised the suspicion of colonic malignancy. Subsequently, colonoscopy and biopsy revealed well-differentiated adenocarcinoma of distal transverse colon (splenic flexure). This case highlights the atypical presentation of colonic carcinoma and need for detailed evaluation in cases where the diagnosis is not apparent.

2. Keywords

Colon; Malignancy; Pleura; Effusion; Adenocarcinoma

3. Introduction

Primary colorectal cancers (CRC) often present with gastrointestinal symptoms such as abdominal pain, weight loss and passage of bright red blood in stools or alteration in bowel habit. Rarely, these tumors may exhibit atypical presentations with symptoms and signs at a site away from the gastrointestinal system, thus resulting in the delay in diagnosis. Chest pain and pleural effusion are uncommon manifestations of CRC. We present a rare case of left exudative pleural effusion which was mistaken for tubercular effusion elsewhere, and on re-evaluation in our hospital was found to be malignant effusion due to carcinoma of splenic flexure of colon.

4. Case Report

A 45 years old lady, house-maker by occupation, was admitted to Tata Main Hospital (TMH) with history of dry cough and pain in the lower left side of the chest for 15 days prior to hospitalization. It was also associated with decreased appetite. There was no history of fever and trauma to the chest. She did not consume alcohol and tobacco in any form. She did not have history of any significant medical ailment in the past.

On admission, she was lean, coherent, had mild pallor, no icterus, pedal edema, and cyanosis. She was afebrile, with pulse rate of 102/minute, blood pressure 130/70 mm Hg, and respiratory rate of 22/minute with accessories mildly working. Examination of respiratory system revealed centrally placed trachea, diminished breath sounds in the left interscapular and infrascapular regions, and few inspiratory crepitations in the same area. SaO2 while breathing ambient air was 95 to 96%. Abdomen was soft. No abnormal masses were felt. However, there was tenderness in the left hypochondrium on deep palpation. Examinations of the cardiovascular and central nervous systems were normal.

Her blood investigations revealed hemoglobin of 9.4gm/dl, total WBC count 15,500 cu mm with 53% neutrophils, 38% lymphocytes, and 9% monocytes, MCV 60.2fl and platelet count 2.35 lakhs/cu mm. Peripheral smear showedpredominantly microcytic red blood cells. Her liver function tests showed total bilirubin 0.6 mg/dl, Alanine transaminase (ALT) 14.2U/L, Aspartate transaminase (AST) 15.6U/L, Alkaline phosphatase (ALP) 76.6U/L, gamma glutamyl transferase (GGT) 24.8U/L, total serum proteins 5.2g/dl, serum albumin 2.2g/dl and globulin 2.9 g/dl, prothrombin time (PT) 19 sec, control 11sec, and PT (INR) 0.99. Renal function tests showed blood urea 38.2 mg/dl and se-

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rum creatinine 1.1 mg/dl. Serum electrolytes were within normal limits. Serum iron was 15.9 mcg/dl, serum ferritin-303.8 ng/ml, serum folate-9.22 ng/ml and serum B12-1092 pg/ml.C-reactive protein (CRP) was 8.29 mg/dl. She was non-reactive for viral markers like antibodies to HIV1 and 2, HBsAg, and antibodies to HCV. Her Mantoux test was negative. Serum carcinoembryonic antigen (CEA) level done by CLIA (chemiluminescent assay) and lactate dehydrogenase (LDH) were respectively 13.9ng/ml (normal< 5) and 2692.4U/L. Her D-dimer assay was 175 ng/ml (normal<250 ng/dl).

Her chest radiograph showed moderate left pleural effusion and mild cardiomegaly (**Figure 1**). Pleural fluid was pale yellow in color. Analysis showed total leucocyte cell count of 1800/cu mm with 10% neutrophils, and 90% lymphocytes. Malignant cells were not found in all 3 samples sent. Microorganisms, acid fast bacilli and fungal elements were not found. Biochemical analysis showed exudative fluid with total proteins 3.33g/dl, albumin 1.69g/dl (SAAG 0.62 which is <1.1), LDH 124.7U/L, glucose 98 mg/dl, and ADA 4.5U/L (>30U/L significant) and amylase 8.2U/L. Pleural fluid cultures were sterile for aerobic and anaerobic organisms. Computerized tomography of the chest (CECT) showed left pleural effusion with partial collapse of left lower lobe. Lung parenchyma was normal. Ultrasound of abdomen showed left sub diaphragmatic collection of the fluid. The rest of the study was normal.

CECT abdomen and pelvis showed diffuse thickening of the colon involving the ascending colon, transverse colon, splenic flexure and sigmoid colon with fistulous tract between the spleen and splenic flexure of the colon with subcapscular collection in the spleen. Multiple air fluid levels were found with collection below the left dome of the diaphragm (**Figure 2**). This raised the suspicion of colonic malignancy.

She was subjected to colonoscopy which revealed thickening, diffuse ulceration and narrowing of the transverse colon with fistula in the distal part (**Figure 3**). Scope could not be negotiated further.

Biopsy taken from distal transverse colonic mucosa for histopathological examination showed invasive well differentiated adenocarcinoma of colon with necrosis (**Figure 4a-c**). Depth of the invasion could not be ascertained.

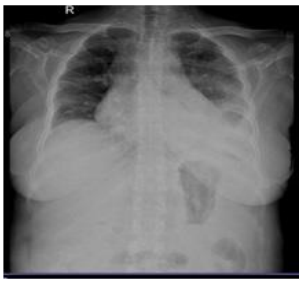

Figure 1: Chest X ray showing left pleural effusion.

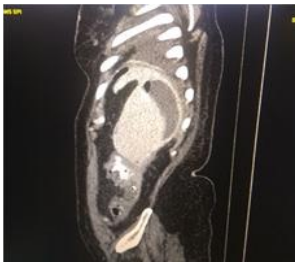

Figure 2: CECT abdomen – longitudinal section showing subcapsular collection in the spleen with air and left sub diaphragmatic collection

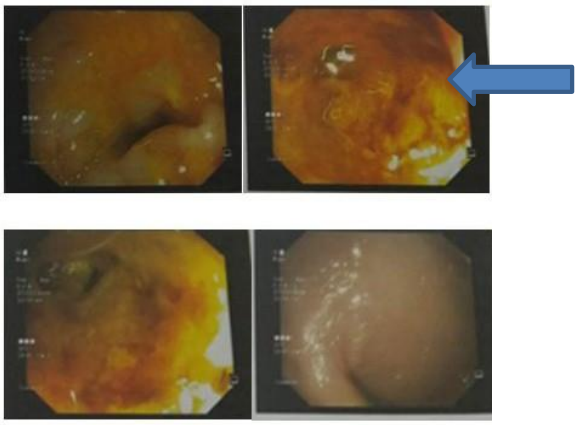

Figure 3: Colonoscopy showing ulcerations and fistula in the terminal transverse colon

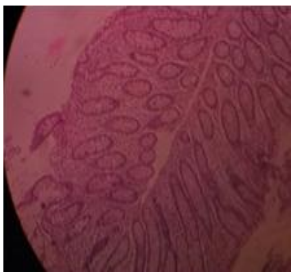

Figure 4a: (H&E X 100) - adjacent fragment shows normal to mildly hyperplastic mucosal glands.

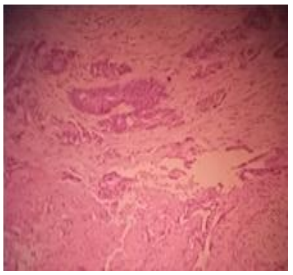

Figure 4b: (H&E X 100) – shows well defined, irregular glands invading into muscularis mucosa.

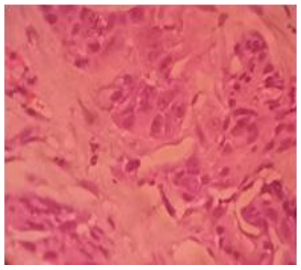

Figure 4c: (H&E X 400) – shows glands lined by pleomorphic epithelial cells with moderate nuclear atypia and vacuolated cytoplasm.

5. Discussion

The common causes of exudative pleural effusion in our country are parapneumonic effusion, tuberculosis and malignancy (pleural or pulmonary metastasis and primary lung cancer) [1]. Together they constitute more than 90% of the causes of exudative pleural effusion. Tubercular pleural effusion is suspected when the pleural effusion is exudate (by Light's criteria) with high Adenosine Deaminase (ADA) levels in absence of underlying pneumonia [2]. Normal value of ADA in pleural fluid is <30U/L. Other causes of exudative effusion include lymphomas, pulmonary infarction, pancreatitis, connective tissue disorders and rarely endometriosis in females.

A raised level of ADA helps to diagnose tubercular pleural effusion with the sensitivity and specificity of 92% (95 % confidence interval 0.90–0.93) and 90% (95 % confidence interval 0.89–0.91), respectively [1,3]. In our patient, pleural fluid ADA value was low with lymphocytic predominance, thus making us think of causes other than tuberculosis. Causes other than malignancy were ruled out from history and relevant investigations. However, no reliable biochemical marker is available toaid the diagnosis of malignant pleural effusion. Low levels of ADA are often used as a surrogate indicator ofmalignant effusion. Also ratio of serum LDH to pleural fluid ADA of >20 (cancer ratio) is highly predictive of malignancy in patients with exudative pleural effusion (whether lymphocytic or neutrophilic) with high sensitivity and specificity [3]. Our patient had serum LDH**:** pleural fluid ADA ratio of 21.6. In a one year retrospective analysis by Verma A et al[1] of 163 exudative pleural effusions, at the cut-off level of >20, the positive likelihood ratio (PLR value) was 32.6 suggesting that patients with malignancy have about 32 fold higher chance of having cancer ratio (Serum LDH: Pleural fluid ADA ratio of>20) compared with patients without cancer. On the other hand, negative likelihood ratio (NLR) at this cut-off was found to be 0.03 which suggests that if the cancer ratio is < 20, the probability that this patient has malignancy is 3%, which is low enough to make the diagnosis of malignancy highly unlikely [1].While cytology is a useful tool in the diagnosis of MPE, it has low yield. Sensitivity of cytology for MPE in multiple case series ranges from 50–90%[4,5].

The patient was admitted to our hospital with symptoms suggestive of respiratory involvement. She had no symptoms pertaining to gastrointestinal system. Prior to her admission in our hospital, she was evaluated outside for 20 days and thus, significant amount of time was spent on finding the aetiology of the pleural effusion. She was empirically started on 4 drug anti-tubercular therapy before she was referred to our hospital. As there was no obvious pneumonia and pleural fluid cultures were sterile, we evaluated her abdomen to rule out intra-abdominal aetiology. A battery of investigations followed which lead to the final diagnosis of malignant pleural effusion (MPE) secondary to colonic carcinoma. Pleural effusion is an uncommon presenting feature of colonic malignancy and hence, can be easily overlooked. It is rarely reported (< 0.9% incidence according to a Chinese database) and mainly occurs in the elderly [6]. However, according to studies by Jonhston et al [7], a Spanish study [8], Agarwal et al [9], and Hausheer and Yarbro et al [10] about 7%,6% and 5% respectively of MPE are caused by gastrointestinal malignancies.

MPE is defined as the accumulation of exudative fluid in the pleural space, accompanied by the presence of malignant cells or tumour tissue [11,12]. Epidemiological information in India is limited, but an estimated 50,000 new diagnoses of MPE are made in the UK each year [11,13]. Mesothelioma is the most common type of primary pleural tumour and is associated with MPE in more than 90% of cases [11,12]. The majority of MPE is caused by metastatic disease: most commonly lung cancer in men and breast cancer in women. These two cancers combined account for 50–65% of all MPE [14]. Other rare causes of MPE are pancreatic carcinoma, colorectal cancer (CRC) and ovarian malignancy in females. According to the American Joint Committee on Cancer and the International Union Centre Cancer (AJCC/UICC), advanced stage IVA CRC is characterized by distant metastasis to one organ or in one site (6,15). Liver is the most common site of haematogenous CRC spread. Liver metastasis occurs in about half of all the cases as colon is drained solely by the portal circulation. Hence, one would not expect metastasis at distant sites without involvement of the liver. Lung is the second most common site of CRC metastasis (15,16). From the lung parenchyma, tumour cells involve the pleura via the pulmonary circulation. Our patient did not have involvement of either. Also by the time, patients with gastrointestinal and gynaecological malignancies develop pleural effusion, they have peritoneal deposits and ascites. Our case was peculiar in the sense that she did not have hepatic, pulmonary and peritoneal involvement clinically and also by computerised tomography.

Similar case was published by Yuan Y et al [17] of 60 year old male who presented with 4 months history of recurrent chest

pain. Pleural fluid was exudate with no malignant cells. On evaluation, patient was diagnosed to have moderately differentiated adenocarcinoma of splenic flexure of the colon. As in our case, patient did not have evidence of hepatic and pulmonary metastasis and ascites. Amongst the intra-abdominal malignancies, intestinal lymphomas, gastrointestinal stromal tumours (GIST) and colo-rectal malignancies can cause pleural effusion. In a four year old study on by Ivan Novakov [6], it was observed that only 12 patients had metastatic colorectal cancer presenting with malignant pleural effusion. Five of them had left-sided effusions while seven had right-sided effusions. All patients had poor prognosis with extremely short survival of 3 to 12 months, depending upon the cell type.

Approximately 35% of colorectal cancer (CRC) patients present with stage IV metastatic disease at the time of diagnosis. The 5-year survival rate for stage IV CRC is less than 10%[18] while that of localized CRC is 90%. The median survival time of patients with stage IV CRC given optimal supportive care without chemotherapy is approximately 5 months [19]. Treatment of metastatic CRC consists of radical dissection, followed by palliative chemotherapy. Pleural effusion responds to chemotherapy. Our patient was referred to higher centre for further management.

6. Conclusion

Elderly patients with left pleural effusion, without apparent diagnosis from clinical examination and preliminary investigations, as in the present case, should undergo thoracic-abdominal CT scans to exclude potential upper abdominal neoplasms. Left sided pleural effusion could be atypical manifestation of gastro-intestinal malignancy. The Serum LDH: Pleural fluid ADA ratio of > 20 should give a clue of the possibility of malignant pleural effusion and further investigations should be directed accordingly.

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