(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 4 , Page No: 610-616
July-August 2022

IJMSCR

Utility of Cryo Lung Biopsy In Picking Up A Rare Diagnosis Of Lymphangitiscarcinomatosa With Unknown Primary – A Case Report

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Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

We describe here a case of occult signet ring carcinoma of the stomach in a 44-year-old female patient presented with dyspnea, weight loss, and fever with a history of exposure to pigeons. Here, autoimmune profile, including RA factor, anti-CCP and ANA profile, came out to be negative. HRCTchest revealed interlobular septal thickening, ground glass opacities, minimal pleural effusion and mediastinal lymphadenopathy. Our differential diagnoses were hypersensitivepneumonitis,sarcoidosis and pulmonary lymphangitiscarcinomatosa. We performed transbronchial cryobiopsy, which revealed clusters of mucin secreting cells with signet ring morphology and appeared to be within endothelium lined spaces suggestive of lymphangitis carcinomatosa.

Keywords: Lymphangitiscarcinomatosa, occult signet ring carcinoma, Gastric carcinoma,Cryo lung biopsy

Introduction

Lymphangitiscarcinomatosis is the malignant aggression and inflammation of lymphatic vessels secondary to the metastatic spread of malignancy from a primary site (1). Carcinomatous lymphangitisis the spread of tumourto thelungsfrom pancreas, colon, stomach, and prostate [2] generally prognosis will be poor.Current literature shows, more survival rate though the pulmonary lymphangiticcarcinomatosis speaks of a terminal cancer stage with low life assumption (4). The diagnosis of lymphangiticcarcinomatosis is challenging due to the negligent symptoms and radiographic abnormalities that shows similarity to interstitial lung disease (5). Most pulmonary metastases are nodular, but a significant minority is interstitial. In PLC, there is deactivating aggression and blockage of pulmonary parenchymal lymphatic tunnels by tumour. Lymphangitiscarcinomatosa describes a condition of diffuse infiltration of the lymphatics of both the lungs by malignant cells. It's reported that Novel chemotherapy achieves rapid symptom control (6).However, improved treatment has increased survival of up to three or more years with treatment.Transbronchialcryo biopsy is a new technique that enables pulmonologists to obtain a larger specimen than the traditional transbronchial forceps biopsy (7). The set back in the diagnosis of PLC can be due to the miscalculation of the proposal andradiographic anomaly by the treating physician**.** (8) PLCpatient who received chemotherapy containing TS-1 and cisplatin achieved a good partial response.

Background

PLC is a metastatic lung that spread through pulmonary lymphatic vessels**.** It is difficult to identify the primary site of malignancy (9).Gastric Carcinoma is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide. It usually presents with anorexia, nausea, vomiting, early satiety, abdominal discomfort, but a presentation with lymphangitiscarcinomatosa is atypical. The invasive nature of the cancer is defined by the speed of proliferation and the ability of invasion/recurrence/metastasis. It at least partially depends on the histological type of primary tumour. Postoperative pathological examination of primary tumour discloses the histological type, degree of invasion, lymphatic and venous involvement, and the lymph node metastasis, and these factors are considered to contribute to the possibility of postoperative recurrence/metastasis. In cancer cases, some viable tumour cells are considered to invade into the lymphatic or veinsfromthe cancer and to disseminate throughout the body. However, most of these tumour cells are disposed of under the host immune system. Remaining tumour cells pass through the defence system and make the metastatic foci in distant organs. It has been reported that cancer cells have a high affinity for sites of vascular endothelial damage, and tumour cells that lodge in a particular organ gradually infiltrate into the parenchyma due to the action of fibrinolysis/coagulation factors and/or VEGF factors (vascular endothelial growth factor).

Case Research: We describe a patient who presented with cough, increased dyspnea, weight loss, and fever with a history of exposure to pigeons. Suspecting hypersensitive pneumonitis, we have subjected the patient to Transbronchial Cryo Lung Biopsy, which yields an entirely perplexing diagnosis of the presence of mucin cells in capillaries. This made usto perform Pan Endoscopy. To our surprise, both UGIE and Colonoscopy were of normal finding. Later we subjected to PET CT, which revealed mediastinal nodal and LungParenchymal FDG uptake. Blind biopsy of gastric mucosa revealed signet ring cell carcinoma, which eventually, IHC evaluation confirmed its origin to Gastric carcinoma.

Case Presentation: A 44-year female, housewife, hyperthyroid with no history of diabetes mellitus, hypertension, coronary artery disease, asthma and tuberculosis, presented to OPD with complaints of dry cough and progressive shortness of breath for 2 months associated with generalized body ache and loss of appetite and weight. No history of travel, no history of sore throat, no history of exposure to COVID patients. Saturation at home is 98% on room air. On careful enquiry, she has a history of pigeon exposure. At presentation, patient was found to have tachypnoea, normal level saturation of 98% on room air, chest auscultation revealed bilateralcrepitations**.** Desaturation was noted on exercise, falling up to 90%. No external signs of malignancy were found. No palpable lymph nodes. Relevant investigations were asked. In view of the ongoing pandemic, COVID-19 was ruled out by RTPCR and CT chest, which revealed thickened interlobular septa, bilateral ground grass opacities, minimal pleural effusion and meditational lymphadenopathy. Then evaluated further, the Thyroid profile was normal. Autoimmune profile, including RA factor, anti-CCP, and ANA profile, came out negative. ECG was normal. 2D echo revealed mild elevated RVSP (35mmhg), mild tricuspid regurgitation. In view of history and the lab findings, hypersensitive pneumonitis is suspected to confirm with histological diagnosis planned for Tran's bronchialcryobiopsy. Cryo Biopsy represents a safe and impressive technique to achieve a larger tissue samples with enhanced diagnostic yield in comparison to standard forceps samples (10).

After explaining possible outcomes, complications and taking informed consent, Trans bronchialcryobiopsy was performed uneventfully, and 4 bits of the biopsy was obtained. Two bits each from the anterior basal and posterior basal segment of the right lower lobe and BAL was collected. No endobronchial abnormalities were found. Obtained biopsy samples sent for histopathology and microbiology revealed clusters of mucin secreting cells with signet ring morphology and appeared to be within endothelium lined spaces suggestive of lymphangitiscarcinomatosis and not suggestive of infection, respectively. The same sample processed for immune-histochemistry came positive for CK20 and CDX2, focal weak positivity with CK7. CD31 and CD34 are seen lining the spaces containing signet cells. As a next step to evaluate malignancy's primary site, Upper GI endoscopy and Colonoscopy were planned and done. Upper GI endoscopy revealed normal study and biopsy obtained from D2 and antrum. Colonoscopy revealed 3 mm polyp in

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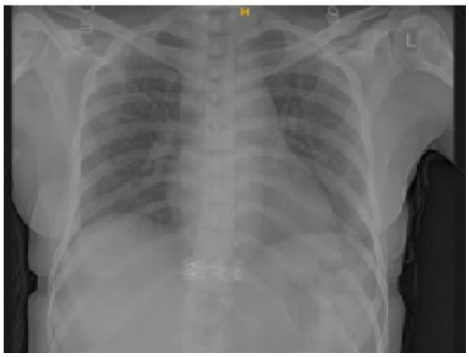
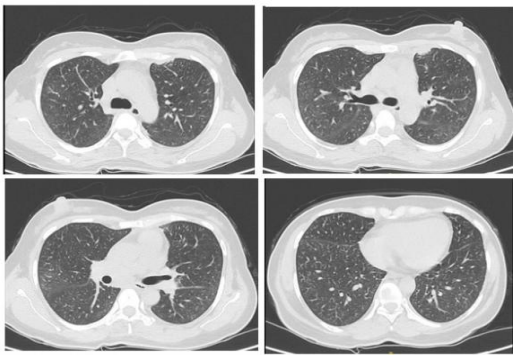
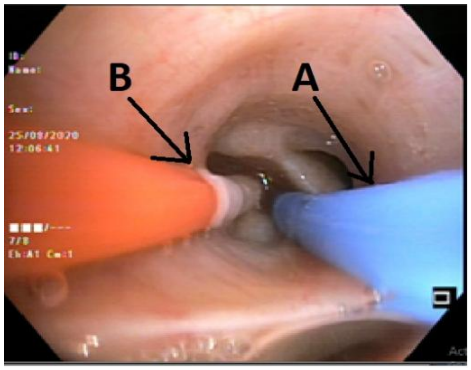
descending colon which was removed in to and biopsy was taken. Biopsy samples from Upper GI endoscopy and Colonoscopy showed signet ring cell carcinoma and tubular adenoma with low-grade dysplasia respectively. Sample was also processed for HER 2 NEU receptor, which was negative. Diagnosis of signet ring cell carcinoma with lymphangitis carcinomatosis was made and to assess the spread, PET CT was done, which showed hyper metabolic node, pulmonary, skeletal, and marrow lesions, but it didn't reveal the primary site. Oncology opinion was taken, and as per her condition and extensive disease patient has been started with FOLFOX 4(5-fluorouracil, leucovorin and oxaliplatin) regimen.

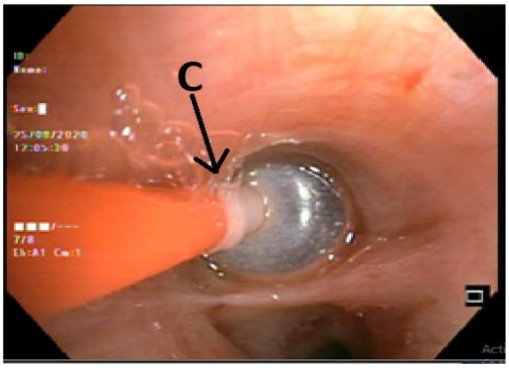


1.CHEST X RAY AP VIEW - BILATERAL GROUND GLASSING AND FINE RETICULAR OPACITIES

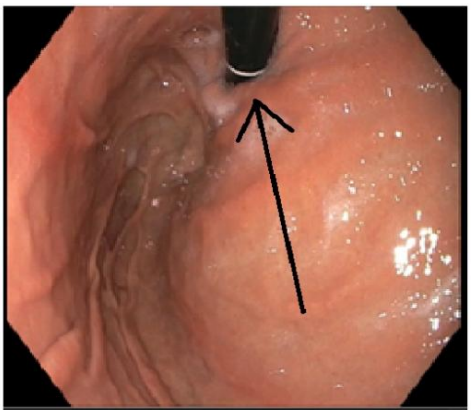


2.HRCT CHEST PLAIN-THICKENED INTERLOBULAR SEPTAE, SUBPLEURAL THICKENING AND BILATERAL GROUND GLASS

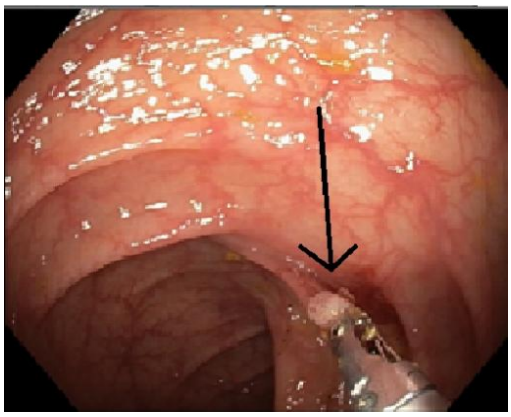




3.TRANSBRONCHIAL CRYO BIOPSY- RIGHT LOWER LOBE, A.ERBE 1.9 MM CRYO PROBE B.FOGARTY BALLOON CATHETER C.INFLATED FOGARTY BALLOON-AFTER TAKING BIOPSYTO CONTAIN BLEEDING.



4.UPPER GI ENDOSCOPY SHOWING - NO SIGNIFICANT ABNORMALITY, BLINDED BIOPSIESWERE TAKEN



B. COLONOSCOPY SHOWING – POLYP IN DESCENDING COLON (BLACK ARROW), POLYPREMOVED IN TOTO

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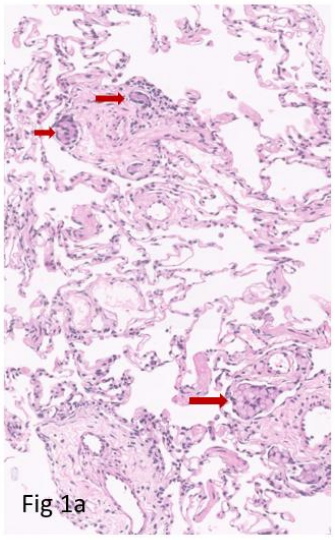

Fig 1a : Lung biopsy showing tiny tumour emboli (red arrows) in vessels with normal lung parenchyma, H&E stain, 20x magnification

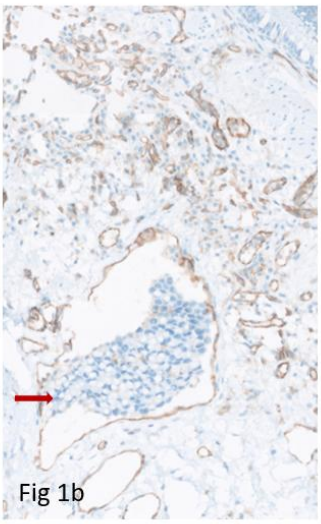

Fig1b: Lung biopsy ,IHC stain CD31,staining the vessel wall with embolus within ,20x magnification.

Fig 1c : IHC stain CK7 staining tumour cells and alveoli, 20X magnification

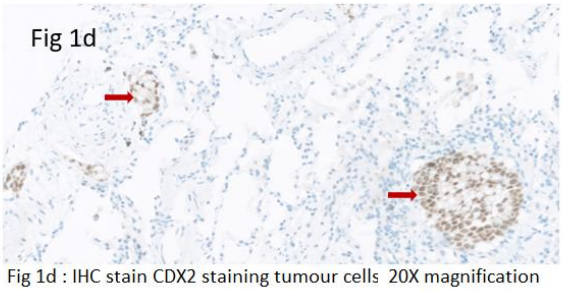

Fig 1d : IHC stain CDX2 staining tumour cells 20X magnification

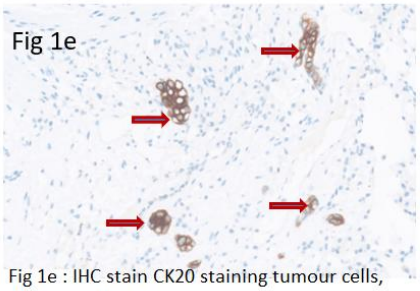

Fig 1e : IHC stain CK20 staining tumour cells, 20X magnification

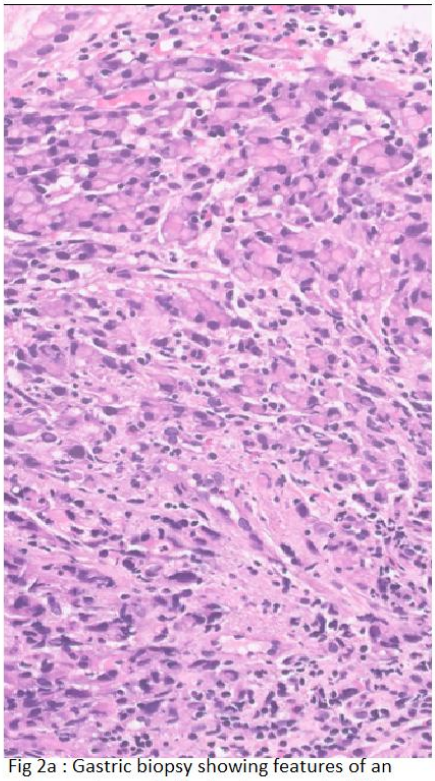

Fig 2a : Gastric biopsy showing features of an adenocarcinoma in the lamina propria, H&E stain , 40X magnification.

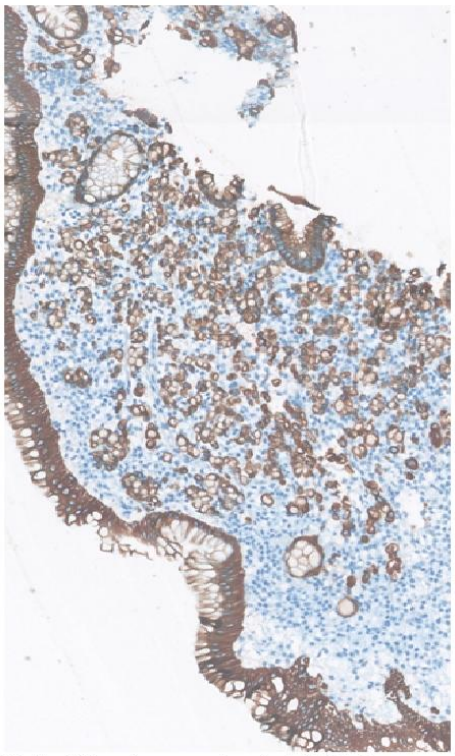

Fig 2b : IHC stain pancytokeratin ,highlighting tumour cells , 20X magnification.

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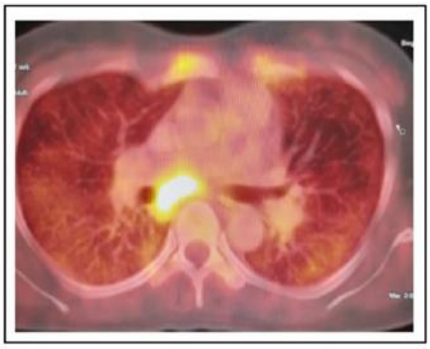

PET Image

Discussion

The first reported case of PLC was by Gabriel Andral in 1829. The usual PLC primary crops up areas are malignancies of the breast, bronchus, and stomach. Cancers of the colon, pancreas, kidney, cervix, thyroid, larynx, and hypopharynx are the other sites with PLCs. Lymphangitiscarcinomatosis is the malignant infiltration and inflammation of lymphatic vessels secondary to the metastatic spread of malignancy from a primary site (11). If the causality dispenses with a typical characteristic feature of the malignancy, the diagnosis will be straightforward. But in patients who presents with pulmonary manifestations of lymphangitiscarcinomatosa with unknown primary, further evaluation should be done through a thorough review of patient`s history and examination and accordingly investigations to be proceeded in search for primary like bronchoscopy guided techniques, upper and/or lower gastrointestinal tract endoscopy, mammography, ultrasound or PET CT. Appearances on a plain chest radiograph include reticular densities, coarsened Broncho vascular markings, Kerley A and B lines, small lung volumes, and hilar lymphadenopathy, but many patients may have normal radiography also . HRCT features suggestive of lymphangiomatosiscarcinomatosaare thickened, often beaded, interlobular septa, sub pleural thickening, pleural effusions, and hilar or mediastinallymphadenopathy. The other findings are nodularity in pleura and ground-glass opacity. Based on radiology, it would be difficult to distinguish from pulmonary oedema, interstitial lung diseases, and sarcoidosis, so detailed clinical examination is essential, and further investigations are always required. Prakash P et al. found that PET CT has more specificity for diagnosing pulmonary lymphangitiscarcinomatosis. The exact mechanism of action for the metastatic spread is not yet understood; the tumour can spread either by i) haematogenous dissemination followed by an invasion of the interstitial lymphatics towards hilum or the periphery of the lung or by ii) retrograde spread of the tumour within the lymphatic channels. It causes compression of the bronchioles and alveoli and thickening of Broncho vascular bundles and septa, leading to dyspnea and cough. It may lead to pulmonary hypertension, pulmonary emboli if PLC is not diagnosed early. If the neoplastic cells spread outside into the lung parenchyma, a nodular pattern can result.

Although these diseases can present with nodular patterns on chest CT scans, the nodules of sarcoidosis are usually confined to the upper instead of the lower lobes in PLC. Post-mortem biopsy analysis show fibrosis and malignant cells.PLC regularly confers in the delayed stages of malignancy. Thetreatment of choice in PLC is chemotherapy.PLC is a metastatic lung disease of malignant tumours that escalates through pulmonary lymphatic vessels (12). Transbronchialcryo lung biopsy is a promising new bronchoscopy technique capable of obtaining best preserved samples when compared with traditional transbronchial biopsy with forceps (13). It shows the importance of cryobiopsy in coming to a diagnosis of occult primary, which preserves tissue architecture. Procedure related mortality and morbidity is less in transbronchialcryo biopsy than surgical lung biopsy. Transbronchialcryo lung biopsy is usually carried with threetypes of probes, which are 1.1 mm, 1.9 mm and 2.4 mm. The most common complications encounter with cryo biopsy is bleeding and

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pneumothorax. To control bleeding bronchial blocker or catheter will be used. Bleeding is more with 2.4 mm probe. Risk for pneumothorax is more, when sample is taken from lower lobe rather than upper lobe. Transbronchialcryo lung biopsy can be performed under mild sedation or general anaesthesia. Chances for pneumothorax slightly higher in intubation patients. Yield of cryo lung biopsy is more when sample is taken from different segments in same lobe rather than same segment (14).In our case, we performed transbronchialcryo biopsy under general anaesthesia via I-GEL withflexible bronchoscopy. We used 1.9 mm cryo probe for biopsy. Fogartycatheter is placed in localised segment prior to the biopsy. We have taken 2 bits each from anterior basal and posterior basal segment of right lower lobe. Maximum diameter of the specimen is 7mm and minimum is 4 mm with tissue freezing time of 6 to 7 seconds. Bleeding is controlled by inflating the fogartyballoon. Post procedure chest x ray revealed no evidence of pneumothorax in our case.

Conclusion

Lymphangiomatosiscarcinomatosa occurs with many different primary tumours and most common lung carcinoma; Signet ring cell carcinoma of the stomach rarely presents as LC. If chest x ray and HRCT chest shows reticularity, a search for primary need to be obtained by performing pan endoscopy and PETCT scan. Our case illustrates rare example of occult signet ring cell carcinoma of gastric mucosa despite pan endoscopy and PETCT scan didn't reveal primary neoplasm. In such a case scenario it is pertinent to perform blind biopsies to achieve the diagnosis**.**

Summary; Troisier, launchedthe term Lymphangitiscarcinomatosa. He described aggression of the lymphatics of lungs by malignant cells. It's prevalence is more in males than the females. At present, there are no successful blueprints to attend to lymphangitiscarcinomatosa. Steroid management may fabricate signalling improvement mainly by relieving SOB. The prognosis remains poor and foretelling of life expectancy is less than one year. With currently available management, it is possible to extend survival up to three years. In pulmonary lymphangiticcarcinomatosis (PLC), tumour cells spread throughout the lymphatic system of the lungs. It is considered a rare end-stage expression of malignancy. A high signal of mistrust is required to diagnose this condition.

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