Case report

Occult pulmonary lymphangitic carcinomatosis presenting as 'chronic cough' with a normal HRCT chest

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Highlights

- Asthma, GERD and postnasal drip are the 3 most common causes of chronic cough.
- Constitutional symptoms (weight loss etc.) never occur in chronic cough.
- Pulmonary lymphangitic carcinomatosis can rarely present with chronic cough.

Abstract

A diagnosis of 'chronic cough' (CC) requires the exclusion of sinister pulmonary pathology, including infection and malignancy. We present a patient with a 3 month history of CC who had an extensive workup including a normal high resolution computed tomography of the chest (HRCT) 6 weeks prior to consultation at our center. He subsequently developed constitutional symptoms including weight loss and loss of appetite 5 weeks after initial consultation. A repeat HRCT chest and a subsequent whole body PET scan found that he had developed extensive pulmonary lymphangitic carcinomatosis (PLC) from a colon primary. Treatment of the colon cancer resulted in significant decrease in metastatic disease burden and cough resolution. PLC is a very rare cause of 'chronic cough' and incipient/occult PLC presenting with chronic cough and a normal initial HRCT chest has not been previously reported.

1. Case

A 66 year old non-smoking Caucasian male with a history of post-nasal drip (PND) and long standing gastroesophageal reflux disease (GERD) presented to our pulmonary clinic for evaluation of a persistent dry cough of 3 month duration. Over the past 3 months, he had failed treatment with inhaled fluticasone/salmeterol, fluticasone nasal spray, omeprazole, loratadine as well as a short course of oral prednisone. He denied wheezing, recent upper respiratory tract infection, fevers, night sweats or weight loss. A chest x-ray (Fig.1) and HRCT of his chest (Fig.2) performed 6 weeks before presentation to our clinic were both normal.

His BMI was 29 kg/M [2] and vital signs were within normal limits. Physical examination was unremarkable. A flexible rhinolaryngoscopic examination revealed some mucus stranding and signs of chronic rhinitis without polyps. Pulmonary function testing (PFT) with methacholine challenge, exhaled oral nitric oxide (FeNO), and sinus CT were all normal. A pH impedance study showed poor symptom correlation to cough along with moderately increased esophageal acid exposure with a DeMeester score of 33.9 (normal < 14.7). A chest CT was not repeated as it had been performed within the past 6 weeks.

Based on the above test results, a treatment regimen consisting of twice daily proton pump inhibitor therapy for GERD and concurrent treatment for PND was undertaken. Several weeks of this regimen resulted in no symptom improvement. A bronchoscopy with random bronchial mucosal biopsies showed chronic inflammation without evidence for infection or malignancy. During a subsequent follow-up visit 5 weeks after the initial consultation, the patient reported new onset weight loss, decreased appetite, and a worsening cough. A repeat HRCT chest (Fig.3) was then obtained and showed interval development of diffuse pulmonary nodules
along with interlobar septal thickening throughout both lungs suggestive of a diffuse hematogenous and lymphangitic metastatic process. New mild bilateral hilar adenopathy was noted without any dominant pulmonary lesion. PET scan revealed intense FDG uptake in the mesenteric wall of the ascending colon with associated wall thickening suggestive of a colon primary. In addition, extensive metastatic disease was noted with FDG avid lesions in multiple lymph nodes in the lower neck, retroperitoneum, skeleton, liver and both lung fields.

A liver biopsy revealed metastatic adenocarcinoma of colorectal origin with immunostains showing tumor cells positive for CK 20 and CDX-2 and negative for CK 7 and TTF-1 (Fig. 4). Palliative chemotherapy was begun with leucovorin, 5-fluorouracil and irinotecan and after several cycles his PLC regressed substantially along with resolution of his cough.

2. Discussion

The term ‘Lymphangitis carcinomatosa’ was first used by Troisier in 1873 to describe diffuse infiltration of the lymphatics of both lungs by malignant cells [1]. It is very uncommon pattern of tumour spread occurring in less than 10% of metastatic cancers in the lung [2]. Most PLCs originate from an adenocarcinoma with primaries frequently noted in the breast, stomach, lung, pancreas, and prostate. PLC may develop in a bilateral symmetric fashion following hematogenous emboli initially lodging in smaller pulmonary arteries and subsequently spreading through the vessel walls into the perivascular interstitium and lymphatic vessels [3]. Asymmetric or localized PLC may result from direct extension of tumour from hilar lymph nodes, pleura or from a primary lung malignancy.

Dyspnea typically develops with an insidious onset often followed by a non-productive cough. These symptoms usually progresses rapidly over weeks and often precede the identification of the primary cause. Chest pain, cyanosis and features of pulmonary hypertension have also been described [4]. Cachexia may accompany respiratory features. Auscultation usually reveals either moist or dry crackles.

Plain chest radiography can be equivocal and non-diagnostic in as many as 50% of the cases. Findings often include Kerley A & B lines, nodular shadows, pleural effusions and hilar lymphadenopathy [5]. HRCT chest scan increases the diagnostic accuracy and is excellent in demonstrating both peripheral and central changes. Common findings on HRCT include thickening of interlobular septa and bronchovascular interstitium giving a characteristic “dot in box” appearance, sub-pleural nodules, and thickening on the interlobar fissures, pleural effusion(s), pleural carcinomatosis, hilar and mediastinal nodal enlargement (40–50%) with relatively little destruction of overall lung architecture [6].

The pathologic features of PLC include distention of the peribronchial and peri-vascular lymphatics with tumour cells often with intra-vascular tumour emboli and endarteritis of the smaller
pulmonary arteries. Neoplastic cells are usually easily identified within the lymphatic spaces, but can also form cords and clusters within the interstitium. The tumor growth can result in spread of the neoplasm outside the interstitium, resulting in the formation of parenchymal nodules [7]. Metastatic cancer in the mediastinal and hilar lymph nodes may obstruct lymphatic drainage, resulting in retrograde migration of cancer cells into terminal lung tissues via lymphatic vessels. Pulmonary function studies will often reveal a restrictive pattern, decrease in lung compliance, gas exchange abnormalities and hypoxemia without hypercapnia [8].

Definitive diagnosis of PLC requires a lung biopsy either via open lung, transbronchial or transthoracic needle approaches [9,10,11]. High yield rates are obtained from either of these approaches and the choice of biopsy procedure comes down to individual patient preferences and circumstances. Treatment of PLC is challenging and overall prognosis is poor with a median survival of 3–6 months from diagnosis [12].

The diagnosis of PLC in our case was delayed due to a combination of nonspecific symptoms, normal initial chest CT findings and a low index of suspicion for malignancy. It is very important to note that the presence of ‘alarm’ symptoms such as fevers, weight loss or loss of appetite is never part of the clinical picture of ‘chronic cough’ with normal chest imaging. The occurrence of these and other symptoms such as hemoptysis or bone pain should prompt an immediate diagnostic workup to rule out sinister pathology. This was especially true in this case where normal chest imaging results (including HRCT chest) had been obtained just a few weeks before consultation. The most common causes of ‘chronic cough’ in patients with normal chest imaging include asthma, GERD, postnasal drip (a.k.a upper airway cough syndrome), ACE inhibitor use and smoking. None of these entities in themselves should cause ‘alarm’ symptoms such as weight loss or loss of appetite. Clinicians should not hesitate to revisit the diagnosis of ‘chronic cough’ in the presence of new ‘alarm’ symptoms and repeat imaging studies should not be delayed even if recently completed as in our case.

3. Conclusion

Occult PLC presenting as ‘chronic cough’ with a normal HRCT chest has not been previously reported in the literature. The development of ‘alarm’ symptoms such as weight loss, loss of appetite or hemoptysis in any patient with chronic cough should be taken very seriously and a comprehensive evaluation should be immediately undertaken to exclude sinister pathologies.

Author contribution

Praveen Jinnur-data collection, writing.
Bibek Pannu-data collection, writing.
Jennifer Boland-pathology slides and interpretation.
Vivek Iyer-writing, review of literature.

Guarantor

Vivek Iyer- I guarantee that the work represented in this case report is unique and has not been published elsewhere. All authors had full access to the data and affirm the decision to pursue publication in your journal.

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Fig. 4. Liver biopsy confirming metastatic disease from a colon primary. Photomicrographs of the liver core biopsy showing metastatic colorectal adenocarcinoma. The tumor is composed of columnar-shaped cells with elongate nuclei forming cribriform glandular structures with central necrosis (A, H&E, 200x), which is very typical morphology for adenocarcinoma arising from colorectal sites. The tumor cells show frank pleomorphism and brisk mitotic activity (B, H&E, 200x). The immunophenotype supports metastasis from colorectal primary site with strong expression of CK20 (C, 200x) and CDX2 (D, 200x) without expression of CK7 and TTF-1 (not shown).
Disclosure

None for all authors.

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