ISSN 0008-3194 (p)/ISSN 1715-6181 (e)/2014/273–279/$2.00/©JCCA 2014

Subtle radiographic presentation of a pleural effusion secondary to a cancer of unknown primary: a case study

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Carcinoma of unknown primary sites is a clinical syndrome that represents many types of cancer. The mortality rate associate to this type of cancer is elevated and a rapid medical referral is required for patients presenting this condition. Pleural effusion may be the only visible sign. We report a case of pleural effusion secondary to a cancer of unknown primary site in a 60-year-old man that sought chiropractic care for radiating low back pain. The radiographic studies revealed a pleural effusion as one of the only significant finding. This article will address the clinical presentation, radiographic studies and a discussion on the radiographic detection of pleural effusion.

(JCCA 2014;58(3):273-279)

KEY WORDS: cancer of unknown primary, metastasis, pleural effusion

Les cancers de sites primaires inconnus représentent un syndrome clinique englobant de nombreux types de néoplasie. Le taux de mortalité associé à ce type de cancer est élevé et une consultation médicale rapide est nécessaire chez les patients présentant cette affection. Un épanchement pleural peut être le seul signe radiographique visible. Nous rapportons un cas d'épanchement pleural secondaire à un cancer de sites primaires inconnus chez un homme de 60 ans qui consultait en chiropratique pour une lombalgie irradiante. Les études radiographiques ont révélé un épanchement pleural comme une trouvaille fortuite. Nous avons inclus la présentation clinique, les examens radiographiques et une discussion sur la détection d'un épanchement pleural.

JACC 2014;58(3) :273-279)

MOTS-CLÉS: cancer d'origine inconnue, métastase, épanchement pleural

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Sources of Financial Support: Dr. Marc-André Blanchette is funded by a PhD Fellowship from the CIHR. Dr. Julie-Marthe Grenier receives no funding.

Introduction

Cancer of unknown primary origin (CUP), or occult primary malignancy, is not a single entity, but rather a complex clinical syndrome that represents many types of cancer. Patients with CUP presents with histologically confirmed metastatic cancer for which the primary site cannot be identified, even following a sophisticated work-up.[1] CUP is not rare, it is the seventh to eighth most frequent cancer in the world[1,2] and represents 2% of all malignancies diagnosed in the United-States[3]. CUP represents the fourth leading cause of cancer deaths in both sexes.[4] The overall age-standardised incidence per 100,000 people per year is 7-12 cases in the USA, 18-19 in Australia, 5-7 in the Netherlands, and 4-6 in Switzerland.[1] The median age at presentation is 59-66 years.[4,5] CUP is slightly more common in men than in women and predominantly affects adults (less than 1% of patient with non-hematologic CUP are children).[4] Patients may demonstrate a wide variety of clinical presentations such as palpable masses, pain or dyspnea, as well as abnormal radiographic findings such as multiple lung nodules and destructive bone lesions.[6]

The natural history of patients with CUP differs considerably from patients with known primary tumours. CUP shows several fundamental characteristics: short history with symptoms and signs associated with metastatic sites, early dissemination in the absence of primary tumour, aggressive clinical course, and occasionally unpredictable metastatic pattern (frequency and location of metastases different from those of known primary tumours).[7] Early dissemination is responsible for the lack of primary tumour-related clinical signs.[4] Additionally, more than 50% of CUP patients have metastatic lesions in more than one location at the time of diagnosis.[4] Optimal therapy for patients with CUP is still under debate and may depend on the histological type of the lesions found: adenomatous, squamous, neuroendocrine or poorly differentiated cell types.[8] The prognosis is poor with an approximate median survival following the diagnosis of 6-9 months.[4] Post-mortem studies have been able to establish that the primary tumours in 73% of patients, the most common primary sites includes lungs (27%), pancreas (24%), liver or bile duct (8%), colo-rectal (7%), genital system (7%) and stomach (6%).[9]

CUP exceeds the scope of practice of chiropractors, however, it is important for clinicians to be mindful that this condition as well as many other cancers initially present with non-specific and vague symptoms. Recognition and quick referrals are key to an appropriate management. This case illustrates this situation well. A review of the history eliciting important details such as dyspnea, loss of appetite; an appropriate examination revealing among other findings, hepatomegaly and a careful observation of important radiographic findings of pleural effusion allowed for a quick referral. Even if the findings of pleural effusion are not specific to CUP, they are serious enough to refer the patient for rapid medical care in order to identify and treat the underlying condition.

Case presentation

A 60 year-old man sought chiropractic care after suffering from episodes of low back pain extending down the left leg for approximately 6 weeks. He described the pain as stiffness that prevented him from walking comfortably or crossing his legs while in a seated position. Initially, the pain was sporadic, but for the last week, it had been rather constant, prompting him to seek care.

Upon further questioning, the patient reported a loss of appetite resulting in a loss of approximately 20 pounds in the last 6 months. He also suffered from insomnia, fatigue and dyspnea. The patient was a long-time smoker. His past medical history included hyperlipidemia, chronic renal failure, myocardial infarction (at age 46). He had been hospitalised for pleural effusion in the past few months. The patient was treated with medication for high blood pressure, anemia, hyperlipidemia, gastric ulcer and prevention of angina.

The orthopaedic and neurological assessment findings were consistent with left sacroiliac joint dysfunction. Nearly all the ranges of motion for the lumbar, hip and knee joints were decreased but none were painful. The vascular examination of the lower limbs was unremarkable.

During part of the examination, the patient was placed in a prone position and signs of facial plethora were noticed. The discoloration faded while the patient was in an upright position and returned each time with a recumbent position. Abdominal and pulmonary examinations were then performed. The liver was found to be enlarged but not tender and the pulmonary examination was within normal limits.

Chest and lumbar radiographs were obtained motivated mainly by the history of unexpected weight loss and

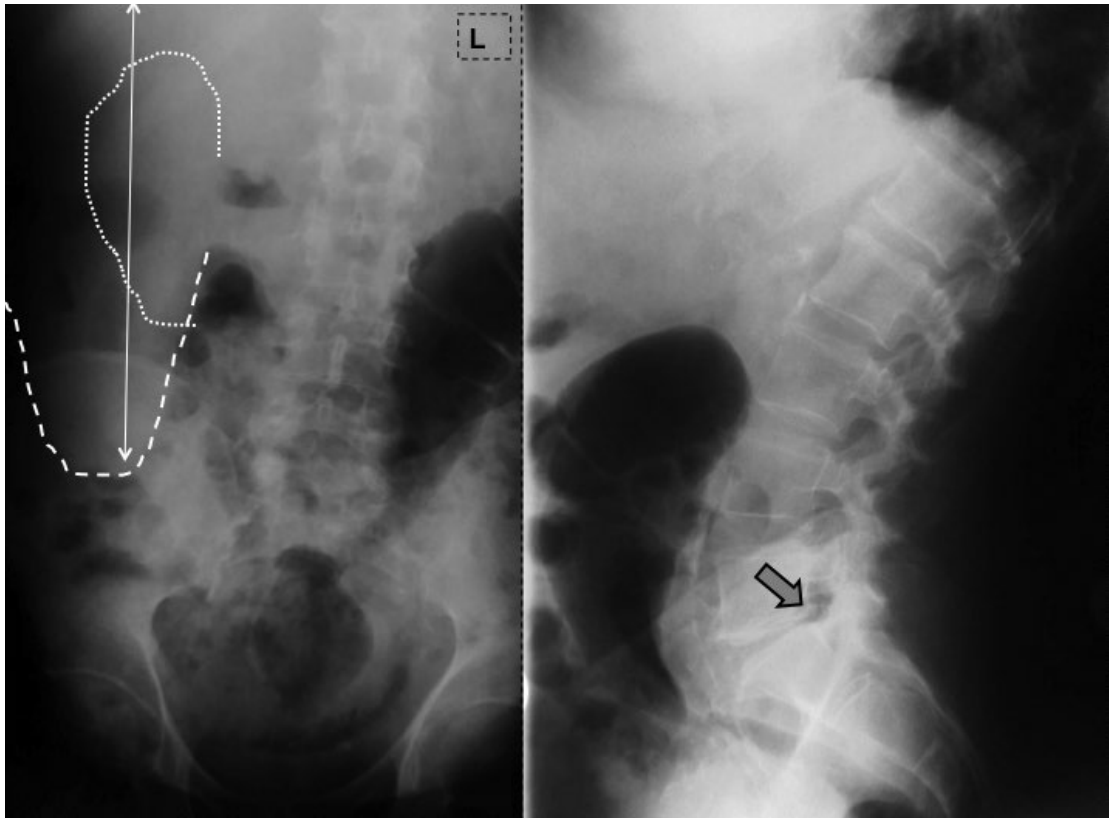

Figure 1:
AP and lateral lumbar radiographs showing degenerative disc disease with posterior osteophytosis at L5 (solid arrow)

Hepatomegaly was also observed, especially on the frontal radiograph. The liver measured more than 16 cm at the midclavicular line. Its medial border extended beyond the right kidney (dotted line) and the inferior lobe extended passed the iliac crest (dashed line).

anorexia combined with the presence of dyspnea, insomnia, malaise and facial plethora.

Radiological findings

Bone density appeared decreased, especially considering the age and body habitus of the patient. Atherosclerotic plaque was visible in the abdominal aorta and the common iliac arteries. Mild degenerative disc disease was present throughout the lumbar spine, but especially involving L5-S1, where a posterior osteophyte was present. Hepatomegaly was also observed, in concordance with the clinical examination. Hepatomegaly is not easily determined on radiographs. Generally, it can be suspected if the liver measures more than 16 cm in length at the midclavicular line on the AP lumbar radiograph and extends below the level of the iliac crest.[10,11] (Figure 1) The liver could not be measured precisely on the radiographs since the superior border could not be seen but its measurement was more than 20 cm. The medial border of the liver as outlined by the air-filled colon also extended past the level of the right kidney, another sign of hepatomegaly.[12]

The chest radiographs (with incomplete field of view due to technical processing damage) demonstrated important blunting of the costophrenic sulci on the right. This is seen on the lateral view with rounding of the costovertebral angle as well as on the frontal view with the disappearance of the right costophrenic angle. The right hemidiaphragm appeared elevated partly because of the accumulation of fluid in the pleural space. This could also be accentuated by the hepatomegaly. (Figure 2) Mild

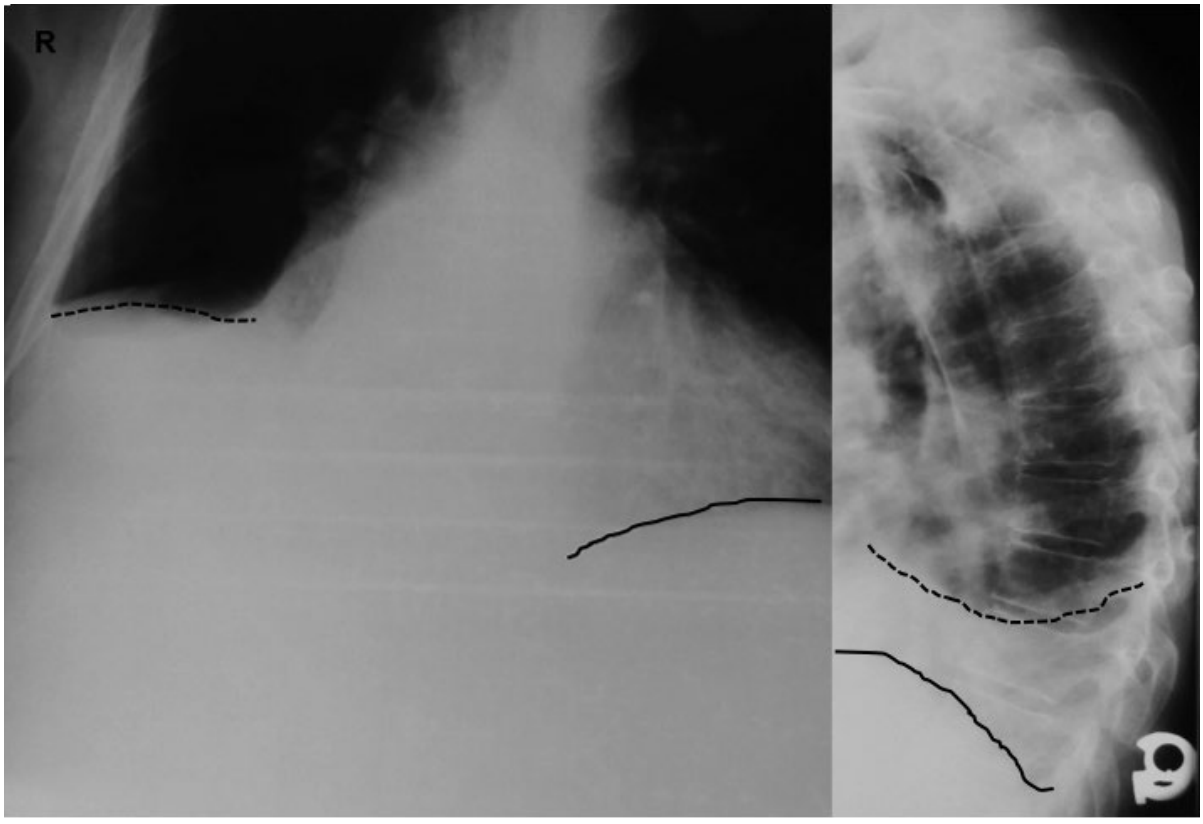

Figure 2:
PA and lateral chest radiographs with incomplete field of view due to technical processing damage.

The right diaphragm (dashed line) appeared elevated on both views.
The posterior and lateral costophrenic angles are rounded on the right side.

blunting of the costophrenic sulci (posterior and lateral) is also noted on the left. The cardiac silhouette also appeared enlarged, when grossly assessed with the cardiothoracic ratio.[13]

The combination of hepatomegaly, mild cardiomegaly and recurrent pleural effusion, along with the past history raised serious concerns about this patient's health status. The patient was referred to the hospital for more assessment and testing.

The patient was hospitalized and underwent a full work-up. The diagnosis of carcinoma with unknown primary source was communicated by the patient's wife to one of the authors during a phone conversation, approximately two weeks after the initial visit. Metastatic lesions had been found in the lungs, brain and bones. The patient was given a grim prognosis: less than one year to live. He passed away two months later.

Discussion

This case highlights the importance of adequately correlating examination with radiological findings. Although the clinical presentation raised serious «red flags» for the presence of disease, the radiological signs were subtle and could have been easily missed, especially if the clinician had omitted to assess the soft tissues. Although the assessment of hepatomegaly on radiograph is imprecise at best, the findings of pleural effusions are relatively easy to visualize if one knows where to look. Chiropractors do not have the necessary resources to diagnose a CUP, but they can recognise a pleural effusion. Pleural effusion is

Table 1:
Causes of pleural effusion[14,17,19]

Transudates	Congestive heart failure
	Cirrhosis with ascites
	Nephrotic syndrome
	Hypoalbuminemia
	Myxedema
	Peritoneal dialysis
	Glomerulonephritis
	Superior vena cava obstruction
	Pulmonary embolism
Exudates	*Malignant*
	Primary lung
	Mesothelioma
	Pulmonary/pleural metastases
	Lymphoma
	Infections
	Bacterial pneumonia
	Bronchiectasis
	Lung abscess
	Tuberculosis
	Viral illness
	Connective Tissue Disease
	Rheumatoid arthritis
	Systemic lupus erythematosus
	Abdominal/Gastrointestinal Disorders
	Pancreatitis
	Subphrenic abscess
	Esophageal rupture
	Abdominal surgery
	Miscellaneous
	Pulmonary infarction
	Uremia
	Drug reaction
	Postpartum
	Chylothorax

not uncommon in patients with CUP, it might be the only visible sign in many patients (as in this case study).[4]

Pathophysiology

The leading aetiologies of pleural effusion are cancer (27%), hearth failure (20%), pneumonia (18%), tuberculosis (9%), pericardial diseases (3.5%) and cirrhosis (3%).[14](table1) The normal pleural space contains a small amount of liquids, which allows the lungs to expand and deflate with minimal friction during respiratory movements.[15,16] Pleural fluid is normally produced by the systemic capillaries of the parietal pleural surface and absorbed into pulmonary capillaries at the visceral pleural surface.[17] Lymphatic vessels also play an important role in removing pleural liquids.[14,15,17-19] There is pleural fluid accumulation whenever the rate of pleural fluid formation exceeds that of its reabsorption. Pleural effusion associated with bacterial pneumonia, bronchiectasis or lung abscess is called parapneumonic effusion, while the presence of pus in the pleural space is named empyema.[17]

According to the composition of the pleural fluid, pleural effusions are classically divided in two type: transudates and exudates.[20] Transudates (low level of protein) occur when there is:

- Increased hydrostatic pressure (e.g.: congestive heart problems),
- Decrease oncotic forces (e.g.: hypoproteinemia),
- Increase negative intrapleural pressure (e.g.: atelectasis),
- Movement of ascitic fluid through the diaphragm (e.g.: hepatic hydrothorax).[14,18,19]

Exudates (high amount of protein) results of:

- Increase in the permeability of the capillary secondary to infection or neoplastic process and/or
- Reduction of lymphatic drainage resulting from obstruction of the latter caused by proliferative (e.g.: malignancy) or inflammatory (e.g.: parapneumonic effusions) process.[14,18,19]

Clinical approach to pleural effusion

The patient history may be very helpful to recognize the signs of pleural effusion and guide the investigation of its potential causes. For example, a typical viral prodrome (low-grade fever, sore throat, upper respiratory symptoms) might indicate a viral pleuritis. A history of congestive heart failure, liver disease, uremia, or malignancy will direct the etiologic investigation of the effusion. Symptoms are often caused by an underling disease and not the effusion itself.[17] Small pleural effusion can be entirely asymptomatic.[14,17] Large effusions will cause dyspnea, trepopnea, with or without chest pain (shooting, dull aching) or dry cough. The chest pain is usually exacerbated by deep inspiration or coughing and may refer to the abdomen or the ipsilateral shoulder.[14,17,21] Trepopnea is a positional dyspnea where the patient has less symptoms when lying of the affected side.[14]

Classic signs during physical examination are: diminished breath sounds, dullness to the percussion, decrease tactile fremitus, and localized pleural friction rub.[16,17] Auscultatory percussion (method of Guarino) might also

Table 2:
Differential diagnosis aids with pleural effusion[14]

Radiological characteristics	Potential Diagnoses
Massive pleural effusion	Malignancy, parapneumonic/empyema, tuberculosis, hepatic hydrothorax
Massive effusion without contralateral mediastinal deviation	Lung cancer, mesothelioma
Bilateral pleural effusion	Heart failure, malignancy, lupus pleuritis and other systemic inflammatory conditions
Located effusion	Parapneumonic/empyema, tuberculosis, hemothorax, malignancy, pleurodesis, plumonary embolism, heart failure
Air-fluid level in the pleural space	Bronchopleural fistula, gas-forming pleuropulmonary infection, spontaneous pneuymothorax, trauma, oesophageal rupture
Foca1 consolidation	Pneumonia, lung contusion, Lung cancer
Apical Infiltrate	Tuberculosis or loculated fluid
Interstitial infiltrates	Heart failure, viral pneumonia, lymphangitic carinomatosis, rheumatoid arthritis
Lung nodules or masses	Malignancy, multifocal infection, rheumatoid arthritis
Pleural calcification	Tuberculous, empyema, asbestos-related pleural disease, trauma
Pericardial calcification	Constrictive pericarditis
Rib fissure or fracture	Trauma

Adapted with permission from Porcel 2013[14]

have some value for detecting small effusion.[22] Many of the patient's medical conditions might have been responsible of the previous hospitalisation for pleural effusion. Among the conditions listed in table 1, the patient had heart and renal failure.

The presence of facial plethora, as demonstrated by this patient is not a classic sign of pleural effusion. It may be a manifestation of retrosternal goiter but may also occur with lung carcinoma, lymphoma, thymoma, or aortic aneurysms.[23] By having the patient in a prone position with both arm elevated on the arm rest, we may accidentally have reproduce elements of the Pemberton's manoeuvre.[24] During this classic manoeuvre, the patient raises both arms above his head as high as possible for one minute. The manoeuvre is positive if the patient experience facial plethora (Pemberton'sign). Pemberton sign occurs when the thoracic inlet becomes obstructed during positional changes, resulting in compression of the jugular veins.

Radiography

Radiographs are the easiest and least expensive way to confirm a clinical suspicion of pleural effusion.[25] Chest radiography may also reveal pleural effusion as an incidental finding. Blunting of a costophrenic angle is the classic sign for pleural effusion. It is important to note that minor blunting may be caused by scarring or chronic atelectasis. Effusions first become apparent on lateral upright radiographs with blunting of the posterior costophrenic angle.[17,19] An accumulation of 200 ml of fluid is necessary for the effusion to affect the lateral angles of frontal standing radiographs.[19,25] Lateral decubitus radiograph with the affected side down is the more sensible view to identify an effusion of 5 to 15 ml.[26] It is possible that effusion unnoticed if the radiograph is taken in the supine position. The fluid then layers superiorly and posteriorly. In this case, an effusion should be considered when there is an opacification of the apical portion of the lung.[19] Other imaging techniques such as ultrasound, CT and MRI may

be helpful in localising effusions and distinguishing transudate from exudates. Table 2 summarizes useful radiographic signs that can guide the investigation for potential diagnosis.

Even if radiography is an effective way to identify a pleural effusion, advance imaging, pleural fluid analysis and when applicable pleural biopsy are key elements to uncover the aetiology of the underlying disease. The role of the chiropractor is to detect the effusion and quickly refer the patient for further investigation. Patients with identified pleural effusion should be referred for medical investigations and treatment since the majority of the underlying condition requires rapid medical attention.

Conclusion

The confluence of findings including pleural effusion led to appropriate referral and diagnosis of CUP. Pleural effusion may be caused by a variety of serious underlying conditions and should be considered in the differential diagnosis of patients presenting with dyspnea, dry cough or trepopnea, with or without chest pain. Pleural effusion might also be an incidental finding on thoracic or lumbar radiography. Chiropractors should look for an asymmetry of the hemi diaphragm, or a blunting of the costophrenic angle on every film where the diaphragm can be visualised. In order to identify and treat the underlying condition, patients should be referred for rapid medical care.

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