

# A 50-Year-Old Man With Pleural Effusion and Chronic Myelogenous Leukemia

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## Abstract

We report herein a case of a 50-year old man who was referred to the respiratory department with 4 months history of progressive dyspnea and dry cough. He was diagnosed to have chronic-phase Ph-positive chronic myelogenous leukemia(CML) 3 years ago and was treated with imatinib since then. Computerized tomography demonstrated a large right pleural effusion, a smaller left one and a small pericardial effusion. Diagnostic thoracentesis revealed an exudative pleural effusion according to the Light's criteria with predominantly lymphocytes. Patient's pleural effusion proved to be imatinib induced, since pleural fluid analysis excluded all obvious causes, discontinuation of the drug resulted in improvement and the patient did not have reaccumulation of his pleural effusion.

## ABBREVIATIONS

ADA: adenosine deaminase

BP: blood pressure

CEA: carcinoembryonic antigen

CML: chronic myeloid leukemia

IFN- $\gamma$ :interferon-gamma

VEGF:vascular endothelial growth factor

RT-PCR: reverse transcriptase polymerase chain reaction

ST1571: imatinib mesylate

## CASE REPORT

A 50-year old man was referred to the respiratory department with 4 months history of progressive dyspnea and dry cough. He was diagnosed to have chronic-phase Ph-positive chronic myelogenous leukemia(CML) 3 years ago. He was treated with imatinib 400mg and allopurinol 300mg daily. He used no other medication.

## PHYSICAL EXAMINATION

The patient was afebrile, with stable vital signs(pulse 83beats/min, respiratory rate 16 breaths/min, BP 130/95mmHg). Chest examination showed significantly diminished breath sounds in the right lung with dullness to percussion, the remainder of the physical examination was unremarkable.

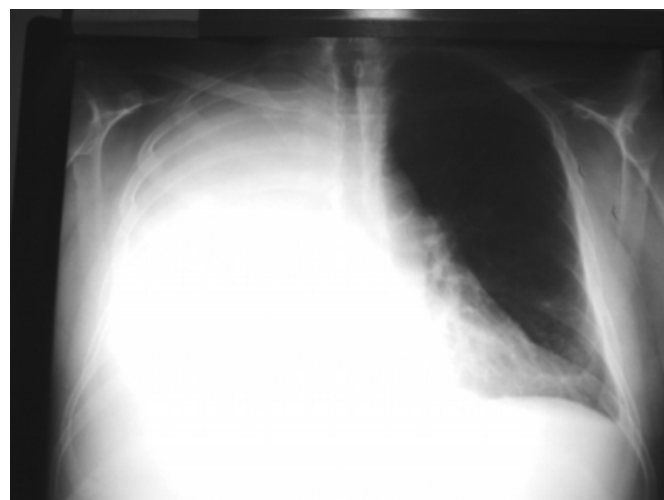
## LABORATORY AND RADIOGRAPHIC FINDINGS

The white blood cell count was 9600 cells/mm<sup>3</sup> with 67.9%

neutrophils, 19.3% lymphocytes, 8.2% monocytes and 2.1% eosinophils. The haemoglobin was 13.6g/dl, haematocrit 40.5 g/dl, and platelet count 169.000 cells/mm<sup>3</sup>. Blood chemistry was all within normal limits. A chest radiograph showed a right large pleural effusion(Fig 1). Spiral computerized tomography demonstrated a large right pleural effusion, a smaller left one and a small pericardial effusion. A diagnostic thoracentesis was performed which revealed straw colored fluid(Fig 2).

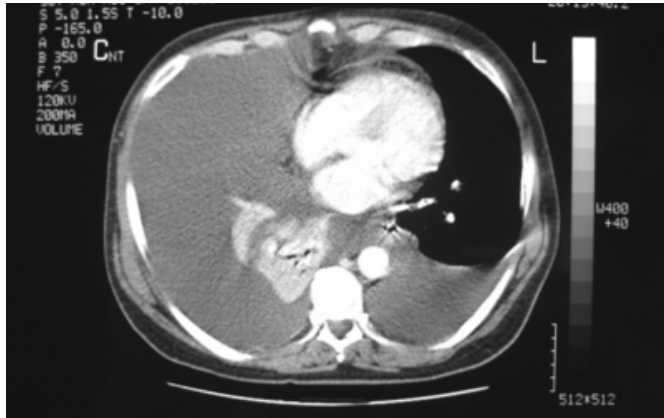
## Figure 1

Figure 1: Chest radiograph demonstrates a right pleural effusion with a mediastinal shift to the left.



**Figure 2**

Figure 2: Spiral computerized tomography shows a large right pleural effusion and a small pericardial and left pleural effusion.



The differential white blood cell count of the pleural fluid showed 10% polymorphonuclear leukocytes, 40% lymphocytes, and 50% mesothelial cells. The biochemical results were the following: pleural fluid total protein 4.65 g/dl (serum total protein, 5.98 g/dl); pleural fluid lactate dehydrogenase 198 IU/L (serum lactate dehydrogenase, 172 IU/L); pleural fluid glucose 156mg/dl (serum glucose, 155 mg/dl). A chest tube was inserted which drained 3 L of this straw colored every day. The antinuclear antibody and rheumatoid factor titers were within normal ranges. Flexible bronchoscopy demonstrated a narrowed right main bronchus and the ipsilateral upper, middle and lower lobar bronchus totally obstructed, due to external compression. Results of bronchial washes microbiological and cytologic studies were negative.

Three separate pleural fluid specimens for cytologic examination proved to be negative for malignancy. The adenosine deaminase(ADA) level in pleural fluid was 10.9 U/L, the gamma interferon(IFN- $\gamma$ ) level was 1.45 IU/ml, the carcinoembryonic antigen(CEA) level was 2.32 ng/ml and the vascular endothelial growth factor(VEGF) level was 325 pg/ml. Their levels in the blood were 17.4 U/L, 1.12 IU/ml, 3.01 ng/ml and 179 pg/ml respectively. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) showed no induction of detectable minor bcr-abl mRNA neither in the pleural nor in the bone marrow granulocytic cells.

A video-assisted thoracic surgery was performed and the obtained biopsy specimen showed inflammatory cells consisted of eosinophils, neutrophils, and plasmocytes. No evident malignant cells could be seen. Imatinib was discontinued and steroid therapy at the dosage of 0.25 mg/kg

was started. There was a gradual remission in pleural fluid production and the chest tube was removed one month after it was inserted and no pleural fluid was reaccumulated.

## DISCUSSION

In our case the patient presented an exudative pleural effusion according to the Light's criteria with predominantly lymphocytes.<sup>1</sup> Tuberculosis, metastatic malignancies including hematologic ones, pulmonary embolization, collagen vascular diseases are the common causes of this picture.

The diagnosis of tuberculosis was easily excluded based on various test results. The pleural fluid ADA level was estimated to be below 40 U/L. Adenosine deaminase is the enzyme which catalyzes the conversion of adenosine to inosine. ADA is a predominant T lymphocyte enzyme, and its plasma activity is high in diseases in which cellular immunity is stimulated. A lot of studies have shown that almost all patients with tuberculosis pleuritis have an ADA level above 40 U/L whereas a pleural fluid ADA level below 40 U per L virtually rules out the diagnosis of tuberculosis.<sup>2</sup> Another test that was used to exclude the diagnosis of tuberculosis pleuritis was the interferon-gamma level in the pleural fluid which proved to be below 3,7 U / ml, the cut off level indicative of tuberculosis pleuritis.<sup>3</sup> Finally the biopsy specimen which was obtained by the video-assisted thoracic surgery did not demonstrate granuloma.

Cytologic examination of three separate pleural specimens of the pleural fluid did not reveal malignant cells. When three separate pleural specimens from a patient with malignant pleural disease are submitted to an experienced cytologist give a positive diagnosis in about 80% of patients.<sup>1</sup> The incidence of positive diagnosis depends on the primary tumor. Most cases of metastatic adenocarcinoma can be diagnosed by pleural fluid cytology. Positive results are uncommon with squamous cell carcinoma because the pleural effusions are usually due to bronchial obstruction or lymphatic blockage. CEA level was below 10 ng/mL which is considered to be the cut off level suggestive of a malignant pleural effusion and VEGF pleural fluid levels were much less than 10 times the serum levels in order the pleural fluid to be considered suspicious of malignancy.<sup>1,4</sup> Thoracoscopy or video-assisted thoracic surgery is the alternative diagnostic approach which establishes the diagnosis of malignancy in about 90% of patients with malignancy. No malignant cells could be seen in the biopsy specimen obtained from our patient.

It is estimated that 4% of patients with myelogenous leukemia suffer from pleural effusion due to pleural infiltration by leukemic cells. Pleural infiltration in CML appears shortly before transformation to acute leukemia and in these cases the pleural fluid contains a variable number of blast cells.<sup>5</sup> In our case white blood cell count was within normal limits and there were no blasts neither in the peripheral blood nor in the pleural fluid. BCR-ABL, a constitutively activated tyrosine kinase fusion protein, is the molecular consequence of the translocation between the long arms of chromosomes 9 and 22 and is considered to be the characteristic genetic abnormality of CML.<sup>6</sup> In our case RT-PCR showed no induction of detectable minor BCR-ABL mRNA neither in the pleural nor in the bone marrow granulocytic cells, concluding that patient's disease was in remission and his pleural effusion could not be attributed to his CML.<sup>5</sup> Finally, the biopsy specimen did not reveal infiltration of the pleura by leukemic cells.

Pulmonary embolization did not seem to be responsible for our patient's pleural effusion since there were not compatible clinical symptoms and signs and the spiral computed tomography did not reveal any partial or complete filling defects. In the same way collagen vascular diseases were excluded based upon patient's medical history and his antinuclear antibody and rheumatoid factor titers which were within normal ranges.

Our last diagnostic approach considered the drug induced pleural effusions. There have been relatively few cases of drug-induced pleurisy, as compared with those involving the lung parenchyma. A drug association is inferred when pleural reaction occurs after exposure to the drug and remits following discontinuation. Onset of clinical symptoms in cases of drug induced pleural diseases ranges from days to years.<sup>7</sup> Imatinib mesylate (Gleevec, STI571, Novartis, Switzerland), a selective Bcr-Abl tyrosine kinase inhibitor is usually well tolerated and has significant anti-leukemic

activity in CML patients. The most frequent adverse events that appear to be related to this drug are nausea, myalgias and cutaneous rashes.<sup>8</sup> Interestingly there are very few cases in the literature where imatinib treatment was complicated with pleural-pericardiac effusion.<sup>9</sup> In our case pleural effusion appeared after 3 years treatment with imatinib. Probably we have excluded any other cause of patient's pleural effusion. Following discontinuation of the drug, pleural effusion resolved and the patient did not have reaccumulation of his pleural effusion

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