

# Coinfection by Mycobacterium Tuberculosis and Mycobacterium Chelonae in a Patient with Hairy Cell Leukemia: Clinical and Therapeutic Management

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## **Abstract:**

**Background:** Hairy cell leukemia (HCL) particularly predisposes to mycobacterial infection due to a number of different reasons. Moreover, HCL clinical presentation may result atypical because of uncommon anatomic involvement and unusual systemic disorders.

**Case presentation:** 59-year-old male, a heavy smoker, with a history of high fever associated with dyspnea and fatigue. Examinations showed mild anemia, leukopenia and thrombocytopenia. Imaging revealed pleural effusion associated with reticulonodular infiltrate with tree-in-bud sign.

Different test on pleural effusion and on pleural biopsy resulted positive for both Mycobacterium tuberculosis and Non-tubercular mycobacteria (Mycobacterium chelonae). Soon after the start of the anti-mycobacterial treatment, the therapy was suspended due to the appearance of a diffuse cutaneous maculopapular exanthema associated with mild dyspnea. Skin biopsy showed a lymph-granulocytic vasculitis. Bone marrow biopsy followed by flow cytometry resulted positive for hairy cell leukemia.

The administration of the appropriate chemotherapy for HCL and the reintroduction of antimycobacterial therapy brought to a prompt remission of fever, dyspnea and skin rash with improvement of laboratory parameters.

**Discussion:** This case is unusual and challenging because of the rare coexistence of HCL, MTB and NTM, the mycobacterial infections preceding instead of following the hematological disease and the uncommon presentation of HCL as a cutaneous inflammatory vasculitis

**Keywords:** Therapeutic Management, Leukemia, Hairy Cell, Mycobacterium Tuberculosis, Mycobacterium Chelonae

## 1. BACKGROUND

Among hematological diseases, hairy cell leukemia (HCL) particularly predisposes either to fungal or mycobacterial infections due to a number of reasons such as neutropenia, impaired neutrophil microbicidal function, monocytopenia, monocyte dysfunction, marked deficiency in circulating dendritic cells and chemotherapy effects [1][2].

On the other hand, HCL presentation may result uncommon with atypical anatomic involvement, autoimmune clinical features (such as vasculitis or arthritis) and other unusual systemic disorders [3].

Here, we report a challenging clinical case of HCL presenting as a cutaneous vasculitis and complicated with a severe coinfection by *Mycobacterium tuberculosis* and *Mycobacterium chelonae*.

## 2. CASE PRESENTATION

On April 16<sup>th</sup> 2018, a 59-year-old caucasian male was admitted to the Infectious Diseases Unit of Garibaldi Hospital in Catania (eastern Sicily) with a 7-day history of high fever (T> 39°C) associated with fatigue and dyspnea.

His past medical history was unremarkable, except for a thalassemia trait. He was also a heavy smoker (40 pack-years).

Clinical examination on admission demonstrated a reduced breath sound in all pulmonary fields. The patient was febrile (T: 38.5 °C), blood pressure was 100/70 mmHg, heart rate was 100 bpm. Oxygen saturation was 97% in room air.

Laboratory examination showed mild anemia (Hb: 11 g/dl), leukopenia (WBC: 3200/mm<sup>3</sup>) and thrombocytopenia (120.000/mm<sup>3</sup>), ESR, CRP and ferritin levels were all elevated.

Chest X-Rays showed a reticulonodular infiltrate in right apical region (sub-clavicle region) associated with organized pleural effusion in left basal region. A CT scan confirmed the presence of multiple nodular lesions, mostly in the right lung, with tree-in-bud sign. A relevant thickening of pleural wall was also seen.

On April 18<sup>th</sup> 2018, a pleural biopsy was performed and a pleural drainage was placed.

Acid Fast Bacilli (AFB) smear, Real Time PCR and culture on pleural aspirate resulted positive for *Mycobacterium Tuberculosis* (MTB). In addition, PCR performed on pleural biopsy tissue resulted positive for MTB. Antibiogram performed on MTB culture in Lowenstein-Jensen medium showed no antitubercular resistances.

Subsequently, Real Time PCR performed on pleural fluid and biopsy showed the presence of Nontuberculous mycobacteria (NTM), in detail, *Mycobacterium chelonae*. On the contrary, no mycobacteria were found in sputum exam.

Anti-mycobacterial therapy was started with isoniazid 300 mg/die orally, rifampicin 600 mg/die orally, ethambutol 800 mg/die orally, clarithromycin 1 gr/die orally, imipenem/cilastatin 2 gr/die iv, amikacin 600 mg/die iv, levofloxacin 500 mg/die iv.

Nevertheless, after two days of therapy, it was interrupted due to the appearance of mild dyspnea (oxygen saturation 92% in room air) together with a cutaneous maculopapular exanthema involving face, chest, abdomen and upper and lower limbs (Figure 1). Oxygen therapy and steroids were promptly administered intravenously.



**Figure 1 - Cutaneous maculopapular exanthema**

Due to the worsening of clinical conditions with a poor response to steroids and the persistence of high fever and maculopapular rash, a diagnostic profile was initiated: serology to Leishmania, Measles, Epstein Barr virus, Cytomegalovirus, Toxoplasma, Parvovirus B19, Echovirus, Coxsackie, Rickettsia conorii, Chlamydia, Mycoplasma pneumoniae and Syphilis were all irrelevant.

Widal-Wright, HIV, Hepatitis B and Hepatitis C virus serology were negative too.

Repeated blood and urine cultures resulted negative as well as laboratory examination for autoimmune diseases.

On 3<sup>rd</sup> of May, a punch-biopsy of skin lesions was performed and histology revealed a lymph-granulocytic vasculitis. RT-PCR on skin biopsy excluded both MTB and NTM.

On 15<sup>th</sup> of May, a bone marrow biopsy was performed. Cells with filamentous surface micro-projections was observed at microscopy. Biopsy showed reduced cellularity associated with maturative distress in erythroid and myeloid series. It showed also an atypical cellular lymphoma-like infiltrate. CD45/SSC gating multiparameter flow cytometry (FCM) was utilized to analyze the immunophenotype; it showed high percentage of B-lymphocytes (98.4 %) expressing as immunophenotypic pattern CD19, CD11c, CD22, CD23, CD25, CD79b, FMC7, CD103. Surface light chains were  $\kappa$  type.

This pattern was suggestive for Hairy Cell Leukemia (HCL).

On 24<sup>th</sup> of May, anti-HCL therapy with Pentostatin 4 mg/m<sup>2</sup> iv was started and anti-mycobacterial therapy was reintroduced as previously (with combined rifampicin, isoniazid, ethambutol, amikacin, levofloxacin, imipenem, clarithromycin).

A progressive remission of fever was obtained with improvement of dyspnea and skin rash. Also, laboratory parameters ameliorated. Within one month from the onset of therapy, chest X-ray demonstrated the disappearance of lung infiltrates and pleural effusions, symptoms completely subsided and inflammatory markers and blood cell count normalized. Comprehensively, 7 cycles of pentostatin therapy were performed.

On 26<sup>th</sup> of July, the patient was discharged giving daily oral home-therapy: rifampicin 600 mg, ethambutol 800 mg, clarithromycin 1 gr, isoniazid 300 mg, moxifloxacin 400 mg, doxycycline 200 mg.

### **3. DISCUSSION**

HCL appears frequently with atypical clinical presentation associated with autoimmune and infectious conditions that may occur both at diagnosis or throughout the course of the disease [3].

The present case is unique because of the coexistence of pleuropulmonary TB and NTM infection as opening manifestations of HCL.

The association between HCL and tuberculosis has been well-studied. In a series of Rose et al, tuberculosis has been reported in 8% of case of HCL [4] occurring either as the first clinical presentation or after chemotherapy [5]. TB reactivation during HCL has been hypothesized to be related to cellular immunity deficiency with particular reference to monocyte-macrophage system abnormalities [6].

Furthermore, hairy cell leukemia has been associated with disseminated NTM disease, as reported in the literature since the early 1980s[7]; a large institutional case series reported an incidence of 5% (9/186)[8] and a survey from Taiwan found more than 1% of patients with hematological malignancy developing NTM infections [9].

It is controversial and yet unclear whether NTM might represent a colonizer or a co-pathogen when associated with MTB. NTM are ubiquitous in the environment and frequently isolated in patients with concomitant pulmonary diseases such as tuberculosis [10].

A significant portion of patients with pulmonary tuberculosis were identified to have clinically irrelevant NTM by Kendall et al, particularly in in case of cavitory lesions[11].

Epstein et al identified different NTM species in 11% of pulmonary tuberculosis patients[12]. Nevertheless, in the present case, the co-occurrence of a hematological tumor and a presumable severe immune deficiency, induced us to consider NTM as pathogenic and potentially life-threatening, thus we treated it together with TB. Some evidences suggest that NTM should always be considered as potentially responsible for lung disease in HCL patients[8][13].

Mixed MTBC and NTM may also present clinical problems for drug susceptibility testing and, as reported by Maiga et al., failure to recognize NTM may lead to misdiagnosis of chronic pulmonary tuberculosis and even to multidrug-resistant (MDR) tuberculosis, especially in developing countries or in pulmonary tuberculosis-prevalent countries [14-17].

A number of reasons make the present case unusual and challenging: the rare coexistence of HCL, MTB and NTM; the mycobacterial infections preceding instead of following (as expected) the hematological disease; the uncommon presentation of HCL as a cutaneous inflammatory vasculitis.

#### **Declarations**

##### ***Ethics approval and consent to participate***

Not applicable

##### ***Consent to publish***

Written informed consent for publication of clinical details was obtained from the patient and it is contained in the patient's clinical record.

### ***Availability of data and materials***

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. We used only information contained in the patient's clinical record.

### ***Competing interests***

The authors declare that they have no competing interests

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### ***Authors' contributions***

- AM wrote the paper
- ST, BMC gave clinical assistance to the case
- ML, AP, VM, DS and FC searched literature references.
- MC, GN and BC revised the paper

All authors read and approved the final manuscript

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