Pulmonary damage in a patient with hairy cell leukemia – infectious involvement or hematological disease activity? Case report

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**Background.** Hairy cell leukemia (HCL) is a rare indolent lymphoproliferative disease with an accumulation of mature B lymphocytes with fine reticular chromatin and cytoplasm with typical hairy-like cytoplasmic projections. Rarely, hairy cell leukemia manifests as a lung infiltration. The differential diagnosis between infection and malignant involvement with hairy cell leukemia is often challenging in such situations.

**Methods and Results.** We present a 53-year-old female with an uncommon pulmonary involvement with hairy cell leukemia. In addition, we discuss the complicated differential diagnosis of pulmonary disease in patients with hairy cell leukemia and the treatment approach to these patients.

**Conclusion.** This case report describes the successful therapy management of a patient with pulmonary involvement by hairy cell leukemia. Therapy with interferon-alfa and cladribine resulted in long-term remission of the underlying disease.

**Key words:** hairy cell leukemia, pulmonary infiltration, interferon-alfa, cladribine

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**INTRODUCTION**

Hairy cell leukemia (HCL) is a B-lymphoproliferative disease with an annual incidence of 0.3 per 100,000 population\(^1\). In the bone marrow and spleen, we find an increased number of mature B lymphocytes with fine nuclear chromatin and hairy protrusions of the cytoplasm. Flow cytometry confirms light chain restriction, expression of CD19, CD20, CD22, CD11c, CD103, CD123, CD25, and CD200. Testing for \(BRAF\) V600E mutation allows us to differentiate variant form of HCL. Consequently, absence of monocytopenia, CD25-, and CD123- is unusual in typical HCL (ref.\(^2\)).

Common indications for treatment of HCL are pancytopenia, fatigue, infections or splenomegaly. Specifically, we indicate a treatment of HCL only when criteria of active disease are met: symptomatic splenomegaly, massive or progressive lymphadenopathy, absolute neutrophil count (ANC) below 1x10\(^9\)/L, neutropenia 1.12 x 10\(^9\)/L, and anemia with hemoglobin 111 g/L. In addition, monocytopenia was present 0.03 x 10\(^9\)/L. The patient did not mention any haematologically significant family history. She was not taking chronic medication at the time of the diagnostic process. The patient did not experience B-symptoms. In manual differential count, we described fine toxic granulation in the granulocytes and atypical lymphoid cells with finer nuclear chromatin and frayed cytoplasm. Consequently, we detected a mutation in the \(BRAF\) V600E gene by molecular genetic testing. Histological examination showed 80% diffuse bone marrow infiltration by medium-sized elements with clear cytoplasm. Subsequently, we detected a mutation in the \(BRAF\) V600E gene by molecular genetic testing. Histological examination showed 80% diffuse bone marrow infiltration by medium-sized elements with clear cytoplasm. Subsequently, immuno-histochemistry confirmed a strong positivity for CD20, PAX5 and DBA44 in pathological lymphoid elements. Bone marrow aspirate flow cytometry confirmed typical expression of CD19, CD20, CD11c, CD103, CD123,
CD25 and partial expression of CD200. Considering these facts, we made the diagnosis of hairy cell leukemia.

The staging ultrasound of the abdomen and peripheral nodes did not demonstrate a lymphadenopathy, splenomegaly or hepatomegaly. A minor, not clinically significant finding was a small liver cyst. To sum up, at the time of HCL diagnosis the patient did not meet the criteria for active disease. Therefore, we utilized watch and wait approach until evidence of symptomatic disease was present.

In November 2015, as part of a planned visit, we newly detected splenomegaly by physical examination (the lower pole of the spleen exceeded 3 cm below the rib cage in inspiration). At the same time, the blood count parameters were stable; therefore we did not initiate the treatment of HCL.

In December 2015, the patient arrived at the local clinic in the Department of Pulmonary Diseases with dyspnea and fever. The patient’s condition required hospitalization. High-resolution computed tomography (HRCT) of lungs, throat cultures and bronchoalveolar lavage (BAL) were performed, which ruled out ongoing bacterial, viral or fungal infection. From July 2017, the patient had clinical manifestations of pneumonia again. Due to the excellent physical condition of the patient, we attempted the treatment first on an outpatient basis. Specifically, we started levofloxacin 1000 mg per day for six days. However, this treatment did not improve the patient’s condition Therefore, the patient was admitted to haematology ward for the progression of fever and fatigue and we extended antibiotic therapy with piperacillin/tazobactam 4.5 g three times a day and clarithromycin 500 mg two times a day in combination for thirteen days.

On admission in March 2016, the patient was found at a concentration of 10⁹/mL. For signs of inflammation and fever, the patient was treated with antibiotics cefotaxime 2 g three times a day and clarithromycin 500 mg two times a day in combination for thirteen days.

In June 2017, the patient arrived after the infectious complication. During the visit, we could not detect clinical or laboratory signs of infection. However, a chest X-ray revealed lung consolidation. To clarify the etiology of pulmonary involvement, we performed bronchoalveolar lavage (BAL), which ruled out ongoing bacterial, viral or fungal infection.

Again, the recurrence of pneumonia in April 2017 required hospitalization in the local clinic in the Department of Pulmonary Diseases. They repeated the HRCT of lungs and throat cultivation, which ruled out viral or fungal infection, but Gram-negative bacteria *Hafnia alvei* was found at a concentration of 10⁹/mL. For signs of inflammation and fever, the patient was treated with antibiotics amoxicillin/clavulanate 1.2 g three times a day and clarithromycin 500 mg two times a day in combination for ten days. Anti-infective therapy led to a complete remission of respiratory problems. At the planned follow-up at our clinic after hospitalization, the patient was completely without symptoms of infection. We initiated a prophylactic dose of valaciclovir 1000 mg daily and cefotaxime 960 mg twice daily on two consecutive days per week. We performed HRCT of the lungs, where we saw a picture of an organizing pneumonia in the right middle lobe and bilaterally inflammatory consolidation around the segments S1, S3 on the right, and S8, S9 on the left. However, we did not detect bacterial, viral or fungal agents in bronchoalveolar lavage. After completing anti-infective treatment, we discharged the patient without clinical signs of infection.

In August 2017, the patient returned with chills, shivering, and dyspnea and elevated inflammatory parameters (CRP 331 mg/L). In the blood count, we found mild leukopenia 3.4 x 10⁹/ L with ANC 1.78 x 10⁹/ L and normocytic anemia with hemoglobin 79 g/L. We performed

### Table 1. Summary of laboratory values over time.

<table>
<thead>
<tr>
<th></th>
<th>White blood cells count (10⁹/L)</th>
<th>Absolute neutrophil count (10⁹/L)</th>
<th>Hemoglobin (g/L)</th>
<th>C-reactive protein (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2015</td>
<td>2.54</td>
<td>1.12</td>
<td>111</td>
<td>3.5</td>
</tr>
<tr>
<td>November 2015</td>
<td>2.76</td>
<td>1.05</td>
<td>110</td>
<td>not available</td>
</tr>
<tr>
<td>December 2015</td>
<td>3.65</td>
<td>2.44</td>
<td>118</td>
<td>460</td>
</tr>
<tr>
<td>January 2016</td>
<td>2.54</td>
<td>1.7</td>
<td>116</td>
<td>0.9</td>
</tr>
<tr>
<td>April 2017</td>
<td>3.22</td>
<td>not available</td>
<td>108</td>
<td>363</td>
</tr>
<tr>
<td>June 2017</td>
<td>3.05</td>
<td>1.7</td>
<td>99</td>
<td>8.1</td>
</tr>
<tr>
<td>July 2017</td>
<td>2.39</td>
<td>1.78</td>
<td>97</td>
<td>332.2</td>
</tr>
<tr>
<td>August 2017</td>
<td>3.4</td>
<td>2.37</td>
<td>79</td>
<td>331</td>
</tr>
<tr>
<td>September 2017</td>
<td>1.68</td>
<td>1.43</td>
<td>70</td>
<td>112.6</td>
</tr>
<tr>
<td>October 2017</td>
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<td>1.79</td>
<td>79</td>
<td>9.7</td>
</tr>
<tr>
<td>March 2022</td>
<td>6.04</td>
<td>4.05</td>
<td>131</td>
<td>not available</td>
</tr>
</tbody>
</table>
HRCT of the lungs again. CT scan revealed infiltrative changes in both lower lobes and diffusely merging focal consolidations with ground glass opacities (Fig. 1). We treated the patient empirically with a dual combination of broad-spectrum antibiotics (meropenem 6 g/day for fifteen days and linezolid 1200 mg/day for eleven days) in combination with the antifungal agent posaconazole 300 mg/day for twenty-two days. We repeated bronchoalveolar lavage with a culture finding of antibiotic-sensitive *Klebsiella pneumoniae* at a concentration of $10^2$/mL. Finally, we performed transbronchial biopsies from lung infiltrates and cryobiopsies. In the histological finding, we described a focal and sometimes even surface infiltration of small lymphoid cells with rich light cytoplasm in the interstitium. No acute inflammatory infiltration was present. There were incipient signs of organizing pneumonia and acute alveolar damage in some alveoli structures. We performed immunohistochemical examination with CD20, DBA44 and ANXA1 positivity (Fig. 2). The finding corresponded to a significant infiltration of the lung parenchyma by hairy cell leukemia. Given that, the patient met treatment criteria. Specifically, indications for treatment of HCL included symptomatic lung involvement and normocytic anemia with hemoglobin values <110 g/L with a repeated need for haemostimulation. We also recommended the administration of subcutaneous filgrastim intermittently due to borderline neutropenia (ANC 1.02x10^9/L). In September 2017, for active ongoing infection, we started treatment with interferon-alpha at a dose of 6 MIU twice a week in an antibiotic cover. After initiation of the therapy, we witnessed a gradual improvement of signs of infection and respiratory insufficiency. We did not report any side effects during interferon-alpha therapy.

During two months of treatment with interferon-alpha respiratory problems disappeared. Additionally, the leukopenia was only mild with leukocytes just below the lower limit of normal. Anemia persisted, but the patient did not require additional haemostimulations. At the beginning of October 2017, we performed a control HRCT of the lungs, where we described a significant regression of bilateral infiltrates.

Following the remission of pulmonary disease, in October 2017, we administered one cycle of cladribine subcutaneously at a dose of 0.14 mg/kg/day for five days. The treatment was tolerated without complications. According to restaging examinations, complete hematological remission was achieved. Moreover, complete normalization of blood counts and lung findings according to the follow-up HRCT of the lungs were achieved (Fig. 3). Nowadays, the patient is without long-term clinical or laboratory manifestations of hairy cell leukemia activity. The patient’s condition improved enough to return to her original employment. The last follow-up took place in March 2022.

**DISCUSSION**

HCL is a disease that predominantly affects bone marrow and spleen. However, HCL may also infiltrate other organs such as liver, skin, and lymph nodes. In our patient, we diagnosed a rare pulmonary involvement by HCL (ref.°). From a differential diagnostic point of view, this is a complex situation. In our case, repeated antibiotics and antifungal treatment of pneumonia did not improve the health condition of our patient. Therefore, we performed a lung biopsy for histological examination. However, a pulmonary biopsy carries a risk of bleeding, traumatic lung damage, deterioration of respiratory parameters or introduction of infection. Given that, it is necessary to rule out infectious complication first. We must also consider other non-infectious causes of pulmonary infiltrates, which can mimic radiologic findings of

*Fig. 1. HRCT of the lungs 8/2017 - ground glass opacities - transversal projection.*

*Fig. 2. Lung biopsy.*

A. significant infiltration of alveolar septa by medium-sized lymphoid elements, hematoxylin-eosin staining, magnification 200x.

B. immunohistochemical detection of CD20, strong positivity in lymphoma population, magnification 200x.

C. immunohistochemical detection of DBA44, strong positivity in lymphoma population, magnification 400x.

D. immunohistochemical detection of mutated form of BRAF (V600E) in lymphoma population, magnification 400x.
pneumonia. Examples of such disorders are inflammatory, drug-induced, vascular and neoplastic diseases.

While searching the literature, we have found several references of lung infiltration by HCL. Vardiman et al. reported autopsy findings in twenty-two patients with advanced hairy cell leukemia. The authors described pulmonary involvement in fifteen cases. However, the infectious lung involvement was present in majority of patients (13/14). In other words, the lung involvement by HCL is a rare condition according to this study.

In addition, we found two case reports on lung infiltration by hairy cell leukemia. The first case report was published in 2019. It describes a 78-year-old man who was admitted to hospital due to exertional dyspnea and pathological changes in the blood count. There was leukocytosis and thrombocytopenia in the blood count, microscopy with the finding of hairy cell leukemia cells. CT scan showed lymphadenopathy in the anterior and middle mediastinum, and ground glass phenomena in lung tissue bilaterally. For persistent dyspnea, bronchoalveolar lavage and transbronchial biopsy from the right central lobe was performed. The pulmonary infiltration by hairy cell leukemia was confirmed. Additional examination revealed the BRAF V600E mutation. The treatment of hairy cell leukemia was initiated with rituximab. After excluding the lung infection, the therapy was completed with a cladribine regimen. The authors observed regression of pulmonary involvement upon successful completion of the treatment. The authors from the USA published a similar case report in 1982 (ref.1).

The treatment of hairy cell leukemia was initiated with rituximab. After excluding the lung infection, the therapy was completed with a cladribine regimen. The authors observed regression of pulmonary involvement upon successful completion of the treatment (ref.7). The authors from the USA published a similar case report in 1982 (ref.13).

The discovery of the purine nucleoside analogs 2'-deoxyformycin (pentostatin) and 2'-chloro-2'-deoxyadenosine (cladribine) significantly improved the prognosis of patients with hairy cell leukemia. With both substances, more than 90% of patients achieved complete remission. Treatment leads to long-term remissions lasting more than ten years. In the Czech Republic, cladribine is the treatment of choice for first-line therapy. We administered cladribine subcutaneously for five days at a dose of 0.14 mg/kg at our department. As cladribine induces severe neutropenia, this medicine is not suitable for patients with active infectious diseases (ref.8). In our patient, we were concerned that administration would exacerbate granulocytopenia. Subsequent pneumonia could result in severe respiratory failure. In the case of a parallel infection, the use of purine nucleoside analogs must be carefully considered, as these antimetabolite agents have a robust immunosuppressive effect. Therefore, in this situation, it is recommended to start treatment with interferon-alfa. Interferon-alfa side effects and hematological toxicity are less dangerous from a comprehensive point of view.

Interferon-alfa is less effective therapy as compared to cladribine in terms of overall response in patients with hairy cell leukemia. Interferon-alfa induces complete remission in only 10% of patients (ref.9). However, interferon-alfa treatment was effective in our patient. There was a significant regression of pulmonary involvement in the underlying disease. Consequently, conditions for the safe administration of cladribine were created.

According to NCCN guidelines for hairy cell leukemia, the role of rituximab in patients with untreated HCL is unclear and is thus generally not recommended as initial treatment (ref.12).

A new study published in November 2021 investigated the efficacy of vemurafenib and obinutuzumab in patients with newly diagnosed HCL. Vemurafenib and obinutuzumab combination therapy induced 100% CR rate with high MRD negativity (96%). The study began enrollment March 2018 and importantly the authors have not observed any relapse to date. But a longer follow-up is needed to assess the durability of remission compared to purine nucleoside-treated cohorts (ref.13).

Patients who are refractory or relapsing after cladribine treatment represent a group of high unmet need. For patients relapsing after more than 24 months, retreatment with purine analog in combination with rituximab is recommended. If the disease relapses within 24 months or the disease is refractory to previous regimen. Monotherapy with rituximab is the treatment of choice (ref.14). According to a multicenter, open-label study of moxetumomab pasudotox, a recombinant CD22-targeting immunotoxin, moxetumomab pasudotox treatment achieved a high rate of durable response and MRD eradication in heavily pretreated patients with HCL. The adverse events of this novel medication were acceptable (ref.15). Similarly, an anti-CD-25 antibody, a BRAF inhibitor (vemurafenib) in combination with rituximab (ref.16) or a Bruton kinase inhibitor ibrutinib are valid treatment options for relapsed HCL.

CONCLUSION

This case report demonstrates the successful management of a patient with rare pulmonary involvement by hairy cell leukemia. Therapy with interferon-alfa and subsequent administration of cladribine regimen resulted in long-term remission of the underlying disease.
ABBREVIATIONS

HCL, Hairy cell leukemia; ANC, Absolute neutrophil count; BAL, Bronchoalveolar lavage; HRCT, High-resolution computed tomography; CR, Complete remission; MRD: Minimal residual disease.

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REFERENCES