Hydroxyurea-induced Pneumonitis in a Patient with Chronic Myelomonocytic Leukemia: An Autopsy Case

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Abstract

We describe the case of an 85-year-old man diagnosed with chronic myelomonocytic leukemia whose disease was treated with hydroxyurea for 3 months. He developed respiratory symptoms that were extensively investigated. Despite the intensive treatment, he died of respiratory failure eleven days later. An autopsy revealed diffuse interstitial inflammation of both lungs consistent with drug-induced inflammation. A drug lymphocyte stimulation test was positive for hydroxyurea. Taken together these findings demonstrated that severe interstitial pneumonitis was induced by this drug. Physicians using hydroxyurea must be aware of its potentially life-threatening pulmonary toxicity.

Key words: chronic myelomonocytic leukemia, hydroxyurea, drug-induced pneumonitis

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder with overlapping myelodysplastic and myeloproliferative features, and an inherent tendency to transform into acute myeloid leukemia (1, 2). Bone marrow (BM) samples in CMML are typically hypercellular with predominant granulocytic/myeloid hyperplasia and dysplasia. Monocytic proliferation is typically present in the BM, but is often very difficult to detect in either the BM aspirate or in biopsy specimens (1). The treatment for CMML is broadly divided into supportive care and directed/targeted therapies, including allogeneic hematopoietic stem cell transplantation (allo-HSCT) (1). Supportive care focuses on symptom management/palliation and applies to patients that are either ineligible for, have failed, or are concurrently undergoing CMML-directed therapy (1). Hydroxyurea (also known as hydroxycarbamide) is a myelosuppressive agent that can help to palliate symptoms related to massive splenomegaly and control elevated blood counts (3). It may cause myelosuppression at higher doses. Other complications include nausea, hepatitis, skin pigmentation, and ulceration. Various pulmonary disorders have arisen from the deleterious effects of drugs on the lungs. Certain cytotoxic agents have been implicated in the production of widespread alveolar damage (4, 5), including bleomycin, busulphan, melphalan and chlorambucil. Hydroxyurea-induced pneumonitis is a rare complication. We herein report a case of hydroxyurea-induced pneumonitis, and present the radiological and histological findings of this disorder.

Case Report

An 84-year-old man presented with exanthema in December 2013. He had no significant medical history except hypertension, and was not being prescribed any medications. Blood tests revealed leukocytosis (21.0×10^9/L) accompanied
had worsened over the previous week. Bilateral basal crepitations and a dry cough, and reported that his symptoms did not reveal the presence of any ground-glass infiltrates of the bilateral lungs. (C) Progressive deterioration of the patient’s clinical condition was reflected by worsened chest radiograph findings on the eleventh day of hospitalization.

**Figure 1.** (A) No pulmonary abnormalities were observed prior to the start of hydroxyurea administration. (B) At the onset of interstitial pneumonia, a chest radiograph revealed bilateral reticular shadows, mainly in the middle and lower regions of the bilateral lungs. (C) Progressive deterioration of the patient’s clinical condition was reflected by worsened chest radiograph findings on the eleventh day of hospitalization.

**Figure 2.** (A) No ground-glass infiltrate was observed before the initiation of hydroxyurea administration. (B) At the onset of interstitial pneumonia, a chest computed tomography (CT) scan revealed bilateral reticular shadows. (C) Chest CT of the thorax at the same level as that shown in A and B, performed on the third day of hospitalization, revealed more extensive ground-glass infiltrate.

by anemia (hemoglobin 9.3 g/dL), and thrombocytopenia (119×10^3/L). The differential blood count showed 3.0% blasts, 20.0% monocytes, 46.0% neutrophils, and 17.0% lymphocytes. The BM was hypercellular and was comprised of 4.4% myeloblasts with dysplasia, and conventional karyotyping revealed 46,XY,add (4) (p11) [19] / 46,XY [1]. Computed tomography (CT) revealed hepatosplenomegaly. From these findings, a diagnosis of chronic myelomonocytic leukemia was made.

The pruritus in the patient’s eczema worsened gradually and the number of monocytes increased. Treatment with hydroxyurea was started at a dose of 500 mg once daily, together with prednisolone 10 mg once daily. Blood transfusion was also started to treat the patient’s anemia. Before the initiation of hydroxyurea administration, a chest radiograph and CT were performed. These diagnostic modalities did not reveal the presence of any ground-glass infiltrates (Fig. 1A, 2A). He was maintained on this dose of hydroxyurea. Three months later, the patient complained of breathlessness and a dry cough, and reported that his symptoms had worsened over the previous week. Bilateral basal crepitations could be heard in his chest. A chest radiograph demonstrated bilateral diffuse shadows (Fig. 1B), and a CT scan demonstrated interstitial change with diffuse ground-glass opacification in a mosaic pattern throughout both lung fields, together with small ground-glass areas in the upper lobes (Fig. 2B). On admission, he was hypoxic, despite being afebrile, and oxygen therapy was promptly started. The administration of hydroxyurea was stopped and the patient was given intravenous levofloxacin. The laboratory findings on admission included elevated serum levels of KL-6 and SP-D (Table 1). A bronchoalveolar lavage (BAL) was performed on admission, but no evidence of infection was revealed either by microscopy or by cultures for bacteria (including mycobacterium), fungi, and viruses. The BAL fluid analysis revealed 122,000 cells/mL (25% macrophages, 73% lymphocytes). The CD4+/CD8+ lymphocyte ratio was 1.38. Cytology (including staining for Pneumocystis jirovecii) was negative, and the results of a subsequent serological test for Legionella pneumophila and Mycoplasma pneumoniae were also negative. On the second day of hospitalization, he was febrile, with a temperature of 39.0°C, and his respiratory
symptoms persisted despite antibiotic therapy. His hypoxia could not be improved with antibiotics. Pulmonary embolism and acute heart failure were excluded. The antibiotic therapy was stopped after four days of treatment due to a lack of improvement and the negative microbiological culture of lavage samples. The patient’s abnormal chest radiograph and CT findings had not improved (Fig. 2C). Treatment with methylprednisolone 1,000 mg once daily for three days was started. Subsequently, he was treated with prednisolone 50 mg once daily. Over the next six days there was a lack of improvement and the negative microbiological culture of lavage samples. The patient’s abnormal chest radiograph and CT findings had not improved (Fig. 2C). Treatments were intermingled, and the acute-phase DAD pattern was predominant. No organization could be detected in the DAD pattern. On the basis of these complex findings, it was not possible to identify a specific subtype of interstitial pneumonia. Clinical investigations suggested that the lung disease may have been caused by hydroxyurea, and this was supported by the pathological findings. In addition to interstitial pneumonia, severe acute inflammation was observed in the bilateral lung, and an abscess was present in the right lung. Histologically, no leukemic cell infiltration was detected. Based on these findings, the severe interstitial pneumonitis was thought to have been induced by hydroxyurea.

### Discussion

Hydroxyurea is increasingly used in the treatment of myeloproliferative disorders because it causes relatively few severe side effects. However, our patient developed life-threatening breathlessness and a dry cough during therapy with hydroxyurea for myeloproliferative disease. Hydroxyurea-induced pneumonia is extremely rare, and only 8 other case reports of hydroxyurea-induced alveolitis or interstitial pneumonitis have been published in the English literature. The differential diagnosis of respiratory disorders in patients with myeloproliferative disease can include common conditions such as respiratory infections, perhaps exacerbated by myelosuppressive therapy, and more specific complications, for example, pulmonary hypertension of unclear etiology (6), or extramedullary hematopoiesis within the lung (7). A precise diagnosis is essential for determining the appropriate treatment.

On rare occasions, acute exposure to hydroxyurea, over a number of weeks, can lead to pneumonitis (8). There are also reports of pneumonitis following chronic exposure (longer than a year) to this drug (9, 10). In the case we report here, hydroxyurea led to this complication after three months of use. On the basis of persistent adverse clinical and radiological findings, despite an abbreviated course of antibiotics, and the findings of the BAL analysis, the presence of DLST (which was positive for hydroxyurea), and the autopsy findings, we concluded that the pneumonitis was due to hydroxyurea rather than a coincidental infectious process. It is not clear whether there were triggering factors.
preceding the development of pneumonitis. Interestingly, cases of hydroxyurea-induced pneumonitis have only been described in patients with an underlying myeloproliferative disorder, which may suggest that an existing hematological condition can contribute to the development of pneumonitis. However, it may simply reflect the fact that hydroxyurea has been extensively used in the treatment of myeloproliferative disorders. Because hydroxyurea is increasingly used to treat
diseases such as essential thrombocytopenia, polycythemia vera, and sickle cell anemia (11-14), cases of hydroxyurea-induced pneumonitis, although rare, may become more common, and it is important to recognize this possibility.

In our patient, the HRCT findings were compatible with a diagnosis of interstitial pneumonitis evolving into pulmonary fibrosis. Such CT characteristics have been well described in drug-induced lung disease (15), although they cannot be used alone to predict a histological pattern or prognosis (16). The autopsy in this case revealed diffuse alveolar damage, and both non-specific interstitial and organizing pneumonia. To the best of our knowledge, this is the first reported case in which an autopsy was performed to investigate hydroxyurea-induced pneumonitis, and we are only aware of eight other cases of hydroxyurea-induced alveolitis or interstitial pneumonitis published in the English literature (8-10, 17-21). The relevant findings from these cases are summarized in Table 2. Only four of these cases described pathological findings, and these were rather non-specific: marked interstitial inflammation with poorly formed granulomas (8), a desquamative interstitial pneumonitis pattern (9), non-specific interstitial fibrosis and pneumocyte hyperplasia (18), and a mixed pattern of cellular and fibrotic interstitial pneumonia with granulomas, consistent with a hypersensitivity reaction (20). The histological responses to pulmonary drug reactions often vary. Drug reactions of the lungs are generally represented through either direct or indirect effects of the drug. We considered the possible causes of the various histological findings in our case (i.e. a complex hydroxyurea-toxic effect, the differing sensitivity of alveolar epithelial cells, or the time course of cellular injury). However, the mechanism of the toxic effect of hydroxyurea remains to be elucidated and further study on hydroxyurea is needed. The BAL fluid contained lymphocytes, which may have been sensitized by hydroxyurea, and could therefore account for the pathogenesis of hydroxyurea-induced interstitial pneumonia. Although eight other patients were alive when their cases were reported, our patient died. The reason for this is unclear. However, our patient was 84 years old and his organ standby capacity was lower than that of patients described in other reports. Although the administration of hydroxyurea was withdrawn and steroids were promptly administered, his physical condition was too poor to allow for a recovery.

The present case highlights the fact that hydroxyurea can lead to severe pneumonitis. This complication, although rare, is important to recognize, as early cessation of hydroxyurea may lead to a substantial improvement in the associated symptoms. The case reported here also demonstrates the possibility of a fatal outcome of this reaction, which mimics an infectious process. Physicians using hydroxyurea must be aware of its potentially life-threatening pulmonary toxicity.

The authors state that they have no Conflict of Interest (COI).

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