CASE REPORT

A 66-year-old man with hydroxycarbamide induced pneumonitis

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ABSTRACT

Hydroxycarbamide is used in the treatment of myeloproliferative neoplasms. Hydroxycarbamide is known for its relative lack of severe side effects.

Here we present a 66-year-old man with a severe pneumonitis within three weeks after starting him on hydroxycarbamide. He developed life-threatening respiratory failure and was admitted to an intensive care unit. Extensive testing of blood and cultures from sputum and bronchoalveolar lavage fluid did not reveal a pathogenic microorganism. Discontinuation of the drug and treatment with prednisolone resulted in clinical improvement within 2 days. Radiological resolution was confirmed after one month. The clinical course suggests that the pneumonitis was induced by hydroxycarbamide.

We want to alert physicians that, in spite of the common assumption that the use of hydroxycarbamide is relatively safe, patients can develop a severe pneumonitis with detrimental outcome and that hydroxycarbamide should be considered a causative agent in the differential diagnosis of pneumonitis.

KEYWORDS

Hydroxycarbamide, myeloproliferative neoplasms, side effects, fever, pneumonitis

What was known on this topic?

Hydroxycarbamide induced pulmonary toxicity is extremely rare. Since 1990 only nine other cases have been described in English literature. Time of onset of hydroxycarbamide pneumonitis after start of treatment can range from two weeks to 12 years.

What does this add?

This case report helps heighten clinical awareness of hydroxycarbamide induced pneumonitis. It is the first Dutch case reported in the literature. Since clinical outcome has a wide variability, it is important to recognise the clinical symptoms. Treatment consists of discontinuation of hydroxycarbamide and prednisolone, although the role of the latter treatment is not well established.

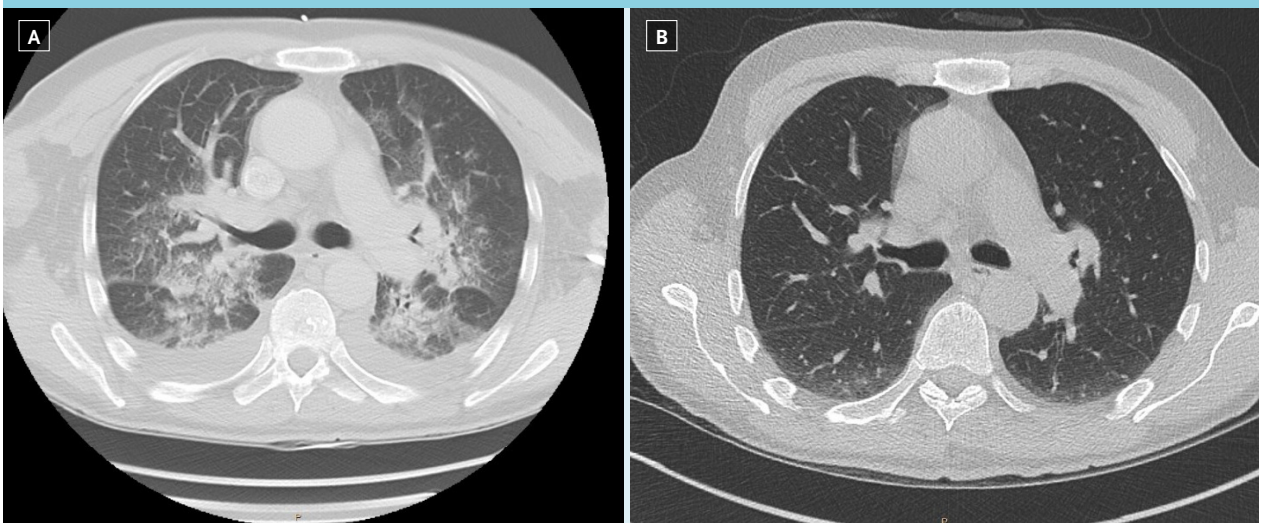
INTRODUCTION

Hydroxycarbamide is well absorbed after oral administration, converted to a free radical nitroxide, and transported by diffusion into cells where it inhibits DNA synthesis by inactivating ribonucleotide reductase, resulting in cell death in S phase.[1] Hydroxycarbamide is widely used in myeloproliferative neoplasms. Although there have been concerns about the mutagenic and leukemogenic potential of the drug, the risk of development of myeloid malignancies is considered to be lower than with other cytostatic drugs.[2] Side effects include pancytopenia, gastrointestinal discomfort and sometimes chronic mucocutaneous ulcers. We describe a patient who developed life threatening respiratory failure with admission to intensive care unit occurring within three weeks after having been started on hydroxycarbamide.

CASE

A 66-year-old man with metastasized prostate cancer and myeloproliferative neoplasia (MPN), was admitted to the hospital because of fever. His medical history included appendectomy and prostatectomy for prostate cancer and superficial thrombophlebitis. Five years before admission JAK-2 (50%) MPN was diagnosed based on a platelet count of 465 x 10^9/l (RW 150-400), elevated haematocrit of 0.51% (RW 0.40-0.50) and normal leucocyte count. Bone marrow

Figure 1. *CT scan images (axial). Figure 1A. Extensive multifocal consolidations with ground-glass. Pleural fluid is extensive Figure 1B. Three weeks after discontinuation, a significant reduction of pulmonary pathology is depicted*



biopsy revealed morphological features compatible with Polycythaemia Vera (PV). Treatment for the prostate cancer consisted of bicalutamide and gosereline.

Because his age of 61 was the only vascular risk factor at the time, he was treated with acetylsalicylate (100 mg/day) and repeated phlebotomies and the initiation of cytoreductive therapy was postponed.

With this treatment haematocrit declined, but platelet counts gradually increased. Because of urinary obstruction a transurethral resection of the bladder neck was planned. In view of the increased risk of postoperative thrombosis due to the combination of hormonal treatment for metastatic prostate cancer, previous thrombophlebitis and JAK-2 driven thrombocytosis (700 x 10^9/l) pre-operative cytoreduction with hydroxycarbamide (500 mg daily) was started.

Nineteen days later he developed a fever and the urologist initiated treatment with ciprofloxacin 500 mg twice a day. Three days later he presented with persistent high fever and was admitted to the urology department and treated with amoxicillin/clavulanate (3 x 1200 mg) in combination with a one-time gift of tobramycin 5 mg/kg.

Next day he complained of dyspnea and fine bilateral pulmonary crackles were heard. The oxygen saturation was 84% (normal > 96%) on breathing room air. Arterial blood gas analysis, on oxygen supply, showed respiratory alkalosis with hypoxemia (pH 7.534; pO_2 7.4 kPa; pCO_2 4.0 kPa; base excess 2.7 mmol/l; bicarbonate 26.7 mmol/l; O_2 saturation 92.1%).

Chest X-ray showed an increase of interstitial fluid (opacity), fluid in fissures and minimal pleural fluid. He received oxygen and furosemide 40 mg intravenously and was admitted to intensive care where he was put on high flow nasal cannula therapy.

Despite a regimen of broad spectrum antibiotics, fever persisted. Cultures from blood, sputum and urine showed no pathogenic microorganisms and urine testing for Legionella pneumophila and Streptococcus pneumoniae was negative. A polymerase chain reaction (PCR) of a throat swab was negative for Influenza A and B and respiratory syncytial virus (RSV), and there was no serological proof for *Chlamydophila pneumoniae, Chlamydophila psittaci, Legionella pneumophila, Mycoplasma pneumoniae* and HIV 1/2. Because of lack of clinical improvement after four days antibiotic treatment was discontinued.

Computed tomography (CT) of the chest revealed extensive multifocal consolidations with ground-glass, bilateral hilar lymphadenopathy and pleural effusion. Examination of fluid obtained by bronchoalveolar lavage fluid showed 40% macrophages, 20.0% neutrophils without malignant cells. Cultures for bacteria, fungi and M. Tuberculosis were negative.

Hydroxycarbamide was discontinued and treatment with prednisolone was started in the dosage of 40 mg/day, within two days resulting in rapid clinical improvement. Patient was discharged from hospital one week later in good clinical condition and prednisolone was tapered and stopped after two weeks treatment. A CT scan performed one month after discharge showed significant improvement (*figure 1*).

DISCUSSION

We describe a patient with life threatening respiratory failure. No pulmonary pathogens were demonstrated and despite broad spectrum antibiotics his condition deteriorated. There was a dramatic clinical improvement

Table 1. *A summary of reports regarding hydroxycarbamide induced pneumonitis*

Reference	Age	Sex	Disease	Hydroxyurea regimen	Radiodiagnostic findings (CTscan/Xray)	Pathology	Period of onset	Symptoms	Treatment	Outcome
1 Jackson 1990[8]	66	Male	CML	500 mg / twice daily	Pulmonary consolidation and pleural effusion	NR	3 weeks	Lethargy, weakness and shortness of breath	Withdrawal and steroids	Recovery
2 Hennemann 1992	77	Male	Myeloproliferative syndrome	500 mg / twice daily	Reticulonodular infiltrates	NR	2 weeks	Fever, dyspnea, hypoxemia	Withdrawal and steroids	Recovery
3 Quintas-Cardama[9] 1999	58	Male	Essential trombocythemia	500 mg / daily	Bilateral interstitial infiltrates and pleural effusion	NR	4 weeks	Fever, hypoxemia	Withdrawal	Recovery
4 Kavuru[10] 1994	78	Female	Myeloproliferative syndrome	500 mg every third day	Peripheral interstitial infiltrates, bilateral pleural effusions	Interstitial fibrosis and hyperplasia of alveolar lining cells	3 months	Dry cough, fever, dyspnea	Withdrawal and steroids	Recovery
5 Sandhu[11] 2000	48	Male	CML	1000 mg 3 times daily (2 weeks) followed by 500 mg / daily	Bilateral interstitial opacities	Interstitial inflammation with poorly formed granulomas	4 weeks	Fever, dyspnea lethargy, pleuritic chest pain	Withdrawal and steroids	Recovery
6 Wong[12] 2003	63	Male	Chronic idiopathic myelofibrosis	1000 mg / daily	Ground-glass infiltrate	Desquamative interstitial pneumonitis	2 years	Breathlessness and dry cough, afebrile, hypoxic	Withdrawal	Recovery
7 Loo 2007	62	Female	Polycythemia rubra vera	500 mg / daily	Ground-glass infiltrate	Mixed cellular and fibrotic inflammation within the interstitium and granulomas	12 years	Non-productive cough and increasing breathlessness on exertion	Withdrawal	Recovery
8 Internullo[13] 2014	77	Female	Essential trombocythemia	500 mg / daily	Fine honeycombing at lungbases, ground-glass at the upper lobes	NR	4 years	Severe dyspnea and respiratory failure afebrile	Withdrawal and steroids	Recovery
9 Hisao Imai[14] 2015	84	Male	CMML	500 mg / daily	Ground-glass infiltrate	3 patterns of interstitial pneumoniae; alveolar damage, non-specific interstitial pneumonia, organizing pneumonia	3 months	Breathlessness and a dry cough, afebrile	Withdrawal and steroids	Dead
10 recent	66	Male	Essential trombocythemia	500mg/ daily	Ground-glass infiltrate, extensive pleural fluid	NR	3 weeks	Fever, respiratory distress	Withdrawal and steroids	Recovery

NR: not reported

after discontinuation of hydroxycarbamide and treatment with prednisolone. The clinical course in combination with the radiologic findings is compatible with a drug-induced pneumonitis. Antineoplastic drugs such as busulfan, bleomycine, chlorambucil, cyclophosphamide, cytosine arabinoside, melphalan, methotrexate, mitomycin and procarbazine have been associated with severe pulmonary toxicity.[3,4] Hydroxycarbamide induced pulmonary toxicity is rare as only nine other cases have been described in the English literature (*table 1*) since 1990. Time of onset of hydroxycarbamide associated pneumonitis after initiation of treatment is highly variable, ranging from two weeks[5] to 12 years.[6] In this patient the respiratory symptoms occurred on the twentieth day after the start of the treatment.

The severity of the clinical symptoms reported is variable. Treatment is not established. Three out of nine patients recovered upon withdrawal of hydroxycarbamide alone. The other six were treated with corticosteroids in dosages ranging from 40 mg to 1000 mg, as in our patient.[5] Most patients recovered, one patient died.

Drug-induced pneumonitis is a diagnosis per exclusionem. A drug lymphocyte stimulation test (DLST) has been introduced as a diagnostic test but its specificity is limited, since a DLST often yields false-positive results.[7] Since the severity of the side effect a rechallenge is not mandantory. We would like to emphasize that, despite the common assumption that the use of hydroxycarbamide is relatively safe, patients can develop a severe pneumonitis with detrimental outcome and that hydroxycarbamide should be considered a causative agent in the differential diagnosis of pneumonitis.

DISCLOSURES

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