CASE REPORT
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A Case of Organizing Pneumonia Following Azacitidine Treatment for Myelodysplastic Syndrome

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ABSTRACT

Organizing pneumonia (OP) is a lung pathology mainly affecting distal lung structures. Its etiology is often unknown, in which case it is termed cryptogenic organizing pneumonia (COP). In cases of OP with an identified cause, the usual culprits include infections, medications, and radiation therapy. In this report, we present the case of a 73-year-old female on azacitidine, a pyrimidine analogue, used for treatment of myelodysplastic syndrome (MDS). The patient presented with fever, productive cough, and pleuritic chest pain. A CT scan of the chest, bronchoalveolar lavage, and transthoracic biopsy were performed, and the findings were consistent with OP, thought to be induced by azacitidine. The patient was treated with prednisone and showed significant improvement. Although rare, this case underlines the importance of considering OP in the context of non-resolving pulmonary infiltrates, particularly when there is a potentially relevant exposure.

LEARNING POINTS

- Organizing pneumonia denotes a distinct pathologic pattern involving the distal terminal bronchioles, alveolar ducts, and alveoli. The associated clinical syndrome is termed cryptogenic organizing pneumonia when no clear cause can be identified.
- The typical associated radiographic pattern is one of patchy, subpleural airspace disease.
- The development of organizing pneumonia has been reported with the use of hypomethylating agents such as azacitidine.
- Low dose azacitidine is used in the treatment of myelodysplastic syndrome and inhibits DNA methylation.

KEYWORDS

Organizing pneumonia, Myelodysplastic syndrome, Azacitidine

1 | INTRODUCTION

Organizing pneumonia (OP) is a lung condition characterized by non-infectious, plug-like lesions of fibroblastic tissue that primarily affect the alveoli and to a lesser extent, the alveolar ducts and terminal bronchioles (1). While the exact pathogenesis of OP is not fully understood, it is believed to develop following injury to the alveolar epithelium, leading to the leakage of plasma proteins and inflammatory cells into the alveolar airspaces, which then promotes repair and fibrosis (1). Many etiologies for OP have been established, including infectious agents (e.g., *Mycoplasma pneumoniae*, cytomegalovirus, SARS coronavirus-2), medications (e.g., bleomycin, methotrexate), radiation therapy, connective tissue disorders (e.g., scleroderma, dermatomyositis-polymyositis), and inflammatory bowel diseases (e.g., Crohn's, ulcerative colitis) (2). These causes should be considered when a new diagnosis of OP is made. In many instances, no injurious agent or event can be identified, in which case the associated clinical syndrome is termed cryptogenic organizing pneumonia (COP) (1).

Histopathological features consistent with OP include the presence of fibroblastic tissue in the distal airspaces and mild chronic interstitial inflammation, with preserved lung architecture (1). Clinical manifestations may include dyspnea, cough, fever, and crackles heard on auscultation while patchy areas of consolidation are common imaging findings (1).

Adverse reactions to many medications, including hypomethylating agents such as azacitidine, have been linked to the development of various forms of OP and other interstitial lung diseases (ILD) (3). Notably, in one reported case, OP was reported following administration of azacitidine for myelodysplastic syndrome (MDS) (3). While this toxicity reaction appears to be rare, heightened clinical suspicion in patients treated with hypomethylating agents for MDS who present with respiratory symptoms is important to ensure timely diagnosis, treatment, and optimal outcomes. More generally, inflammatory lung conditions such as OP (with or without a putative inciting agent) should be considered in immunosuppressed patients who fail to respond to antibiotic treatment despite presenting with signs and symptoms suggestive of an infectious lung process – even more so if focused investigations such as bronchoscopic sampling do not yield an infectious cause. We describe the case of a female with MDS who developed clinical and radiographic findings compatible with OP after administration of azacitidine. The patient has provided written informed consent to review and share her case information.

2 | CASE DESCRIPTION

We present the case of a 73-year-old female with essential thrombocytosis (ET) progressed to a JAK2-mutated myelodysplastic syndrome (MDS). She began azacitidine treatment for her MDS in March 2019, with monthly cycles involving 7 consecutive daily doses. The patient also had a history of stasis dermatitis, nummular eczema, rosacea, a previously resected squamous cell carcinoma of the nose and scalp, sciatica, Sweet syndrome, and irritable bowel syndrome. Home medications included pregabalin, pantoprazole, and valacyclovir, none of which is known to be associated with lung disease, including OP (4).

Shortly after administration of the 23rd cycle of azacitidine, the patient developed a fever and experienced chills and rigors. The symptoms persisted for seven days, after which the patient presented to the hospital, reporting fever, chills, productive cough, and right-sided pleuritic chest pain. Physical examination was significant for a temperature of 38.4°C, heart rate of 125 beats per minute, and mild bilateral basilar crackles on lung auscultation.

A chest x-ray demonstrated right-sided abnormalities, including an upper lobe para-mediastinal opacity, nodular opacities at the base, and a small pleural effusion. Moreover, an initial CT scan of the chest (Figure 1a) revealed bilateral, predominantly subpleural, irregular solid nodules with ground glass halos in addition to a mild small right pleural effusion. Cultures of the patient's blood and urine failed to grow any pathogens. Cytomegalovirus (CMV) DNA was undetectable in the

serum, and serum antigen testing for Cryptococcus, Galactomannan, Blastomycosis, Mycoplasma were all negative. The patient also tested negative for SARS-CoV-2. Other notable laboratory findings included an elevated C-reactive protein (CRP) of 68.7 mg/L, slightly elevated absolute neutrophil count, a microcytic anemia, with leukocytes and platelet counts within the normal range. Given the patient's suppressed immune state in conjunction with the clinical, laboratory, and imaging findings, pneumonia potentially related to an opportunistic pathogen was initially considered the most likely diagnosis. Hence ceftriaxone, azithromycin, and isavuconazole were started empirically.

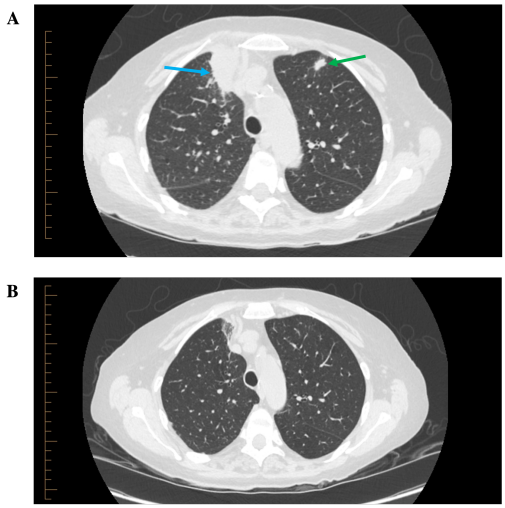

FIGURE 1 CT of the chest before and after treatment with prednisone.

(A) Representative CT chest image on admission. The image shows a dense, subpleural mass-like lesion in the right upper lobe in paramediastinal location (blue arrow), as well as a small nodular opacity in the left upper lobe (green arrow). The right upper lobe lesion was biopsied. (B) CT chest image from same level, one month after initiation of prednisone. The right paramediastinal mass-like lesion has substantially decreased in size and density. The left upper lobe lesion is no longer visible.

As the patient did not improve clinically, further investigations were conducted, including a bronchoalveolar lavage (BAL) and a CT-guided transthoracic lung biopsy of the right upper lobe. The BAL cellular analysis showed mainly inflammatory cells and minimal T-lymphocytes. The tissue biopsy only showed inflammatory changes, without the presence of neoplastic cells (Figure 2). As depicted in Figure 2, the tissue obtained from the biopsy was stained with hematoxylin and eosin and displayed polypoid fibroblastic aggregations in alveolar sacs (as indicated by the arrows) in addition to reactive changes in the alveolar epithelium. Neither specimen showed *Pneumocystis jiroveci* or any other fungal or viral organisms.

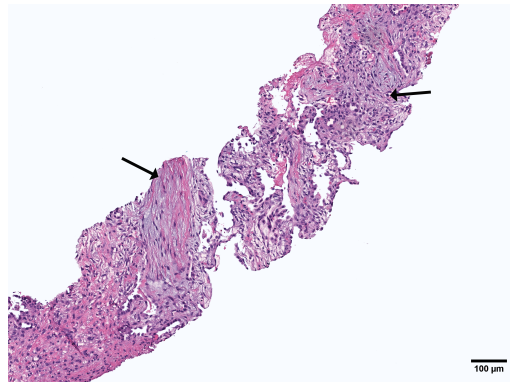

FIGURE 2 Hematoxylin and eosin-stained tissue from patient's transthoracic lung biopsy of the right upper lobe.

The lumens of the alveoli and alveolar sacs are filled with polypoid fibroblastic aggregations (arrows). The lung alveolar epithelial cells show reactive changes. Digital images are prepared using the Aperio AT2 scanner at a 200X magnification.

Based on the new findings, an ongoing infectious process was deemed unlikely, and with input from respiratory consultants, a provisional diagnosis of drug-induced organizing pneumonia was suggested. The patient was started on 50 mg of oral prednisone daily, with rapid symptomatic and radiographic improvement. A repeat CT of the chest (Figure 1b), obtained four days after the start of prednisone treatment, showed partial regression of the parenchymal lung disease. The patient was subsequently discharged and followed up in the respirology outpatient clinic, with gradual tapering of her prednisone. Her organizing pneumonia syndrome was attributed to the azacitidine, which was consequently stopped and replaced with decitabine-cedazuridine, an

alternative treatment for MDS.

3 | DISCUSSION

In the past two decades, hypomethylating agents (HMA) such as azacitidine have become the preferred treatment option for patients with high-risk MDS who are not eligible for more aggressive chemotherapy or stem cell transplantation (5). At the low doses prescribed for the treatment of MDS, azacitidine acts as a nucleoside analogue that inhibits DNA methyltransferase, leading to DNA hypomethylation (5). These molecular events activate tumor suppressor genes, which are thought to be silenced via hypermethylation, creating a favourable tumor-suppressing environment (6). While azacitidine is generally safe, adverse events have been associated with its use (7). Unlike other chemotherapeutic agents, these side effects do not result from cumulative dosage, but are most frequent and severe following treatment initiation, with marked improvement over time (7). The most common hematologic toxicity is cytopenia, while the most common non-hematologic side-effects are related to the gastrointestinal system (7). Mild fever and fatigue can also occur (7). Rarer toxicities, such as respiratory dysfunction and necrotizing fasciitis, have been reported (8)(9). Alnimer et al. reported a patient who developed respiratory symptoms one week after receiving their second cycle of azacitidine and was diagnosed with organizing pneumonia, similar to our patient.(3). They also discussed six other known patients who developed OP following administration of HMAs (3). Of note, four of them developed symptoms within the first two cycles of treatment (3). Toxicities and adverse events after prolonged use of azacitidine are sparsely reported in the literature. One rare instance shows clinical progression of ischemic heart disease following 60 cycles of azacitidine (10).

To our knowledge, this is the first patient reported to have developed symptoms and signs of organizing pneumonia after a long course (23rd cycle) of azacitidine. The following elements support a diagnosis of azacitidine-induced OP including exclusion of infectious, neoplastic, and medication-induced causes, temporal relationship between symptom onset and HMA administration, radiographic findings (multiple subpleural irregular nodules), histopathological results, and a favourable response to prednisone. Importantly, as there is no consensus on the optimal number of azacitidine cycles needed to treat MDS, treatment duration varies widely in the literature. One study examining patients with high-risk MDS found that a median of 14 cycles was necessary for those who responded positively to treatment (6). While most patients showed a favourable response early on (after 6 cycles), optimal response was achieved only with continued use (6). As such, continuous management of MDS with azacitidine is recommended for patients with strong response who do not experience adverse effects (6).

We recognize that many of the side effects associated with HMAs typically occur early in the treatment course and that short courses of pharmacotherapy are responsible for most drug-induced cases of OP (11). However, it is possible that the development of respiratory symptoms seen early in azacitidine treatment reflects an immediate, idiosyncratic injury and reaction, while the events in our patient resulted from cumulative toxicity, eventually reaching a threshold sufficient to cause pulmonary injury. We hypothesize that prolonged use of azacitidine may lead to gradual tissue accumulation and late toxicity. Delayed lung toxicity has been observed with other drugs (12). In one case, a 64-year-old female was diagnosed with an OP secondary to amiodarone treatment, a medication she had taken for four years to treat atrial fibrillation (13). Similarly, following long-term prophylactic treatment with nitrofurantoin for urinary tract infections, a 82-year-old female developed OP which improved after cessation of the antibiotic (14). However, the potential for toxicity resulting from tissue accumulation after chronic azacitidine use has yet to be clarified. A phase-1 study reported no toxicity following azacitidine administration, although it included only 29 patients who had completed a median of six cycles for MDS, so the possibility of later, dose-related toxicity could not be excluded on this basis.

Another study examined mononuclear cells ex-

tracted from the bone marrow of patients newly diagnosed with MDS at baseline and after the fourth and eighth courses of azacitidine treatment (16). Following treatment, the extracted mononuclear cells exhibited azacitidine-induced autophagy, a regulated, lysosome-dependent cellular degradation mechanism that plays an important role in acute and chronic inflammatory lung processes (16). For instance, autophagy-associated proteins have been shown to be highly expressed in patients diagnosed with hypersensitivity pneumonitis (17). To our knowledge, the specific role of autophagy in OP particularly in the context of azacitidine treatment has yet to be explored, but it represents a plausible mechanism of tissue injury that merits further investigation.

4 | CONCLUSION

We present a case of azacitidine-induced pulmonary toxicity in the context of MDS treatment. We posit that the destruction of alveolar epithelium leading to the development of OP following azacitidine treatment may conceivably reflect different mechanisms, including toxic accumulation and autophagy. This case highlights the importance for clinicians to remain vigilant for this rare but toxic side effect. More generally, physicians should bear in mind the potential for non-infectious etiologies, including drug-induced inflammatory conditions, when patients with apparent pneumonias do not evolve as expected.

5 | CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

6 | AUTHOR'S CONTRIBUTIONS

All authors read and approved the final manuscript.

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