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Original Research Paper

Pulmonary Medicine

A RARE CASE OF ORGANISING PNEUMONIA ASSOCIATED WITH AZACITIDINE THERAPY

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ABSTRACT 48 year old patient with Myelodysplastic syndrome, presented with breathlessness, fever, cough after azacitidine. Broad spectrum antibiotics and antifungal therapy failed to show any improvement. HRCT chest showed right pleural effusion with ground glass opacities, perilobular pattern of septal thickening.

He was given oral prednisolone [40 mg per day], tapered over 3 months. Repeat imaging showed near complete resolution.

DISCUSSION: Interstitial pneumonitis is a rare adverse reaction to azacitidine, a pyrimidine analogue used to treat MDS, with only six cases reported [2 cases of organising pneumonia].

The HRCT chest finding of perilobular interseptal thickening with right side effusion is consistent with organizing pneumonia.

Negative pleural and blood cultures ruled out infective etiology.

Treatment with steroids lead to improvement.

CONCLUSION: Drug induced pneumonitis has a potential to be reversed if diagnosed in time and needs to be kept in mind while treating patients of MDS with azacitidine chemotherapy.

KEYWORDS : azacitidine, organising pneumonia, myelodysplastic syndrome, drug- induced lung disease

Introduction

As we venture into the new territory of chemotherapy for hematological disorders, the use of these agents tends to become a double edged sword. The adverse drug reactions become difficult to diagnose due to lack of clear guidelines and the manifestations overlapping with either the primary disease progression or infectious etiology. We present an extremely rare case of cryptogenic organizing pneumonia following therapy with azacitidine. Although this drug is commonly well tolerated and rarely causes severe lung injury, it is important to consider the potentially serious adverse effects of azacitidine-induced pneumonitis.

Case report

A 48 year old gentleman, a diagnosed case of myelodysplastic syndrome [MDS] presented to us with symptoms of fever, nonproductive cough, pleuritic chest pain and shortness of breath since 2 weeks. On examination, he had signs of a right sided synpneumonic effusion with a few scattered crepts on the left side. The chest X-ray showed a right lower zone consolidation with pleural effusion. A thoracocentesis was done and he was started on empirical antibiotic therapy. He had pancytopenia with haemoglobin of 6.6 gram percent, and the white blood cell [WBC] count was 3200 cells per cubic millimetre and platelets were 30000 cells per cubic millimetre. The pleural fluid was exudative with lymphocytic predominance, but Adenosine Deaminase levels were low and bacteriological investigations on the fluid were negative. Cartridge based Nucleic acid amplification test (CB-NAAT) for Mycobacterium Tuberculosis [M.Tb] was also negative on both sputum and pleural fluid samples.

A high resolution computed tomography [HRCT] was done which showed pleural effusion on the right with fissural extension, bilateral ground glass opacities [GGOs] and interstitial thickening, with consolidation in the right lower lobe [figure 1].

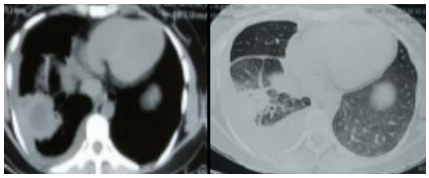

Figure 1: Right Lower lobe organising pneumonia with pleural effusion.

He did not respond to the empirical antibiotics and the fever persisted so antifungals were added empirically on day 7.

The blood cultures were negative and there was no improvement in WBC and platelet counts. A bronchoscopy to confirm the diagnosis was planned but the patient refused the procedure.

The patient was on treatment for MDS since 5 years and had been started on azacitidine [1st cycle for 7 days] 1 month prior to onset of symptoms. He had previously received lenadolamide, which had led to a remission for 2 and a half years. Due to repeat thrombocytopenia, lenadolamide was stopped and he received decitabine for 3 cycles, but did not respond. Azacitidine was initiated 5 months after the decitabine. He had also received multiple platelet transfusions in view of severe thrombocytopenia.

In view of the declining platelet counts, he was started on pulse steroid therapy under the cover of antibiotics, antifungals and antiviral drugs. The steroids were tapered gradually after 3 months. Blood investigations were repeated which showed an increase in the platelet counts following the steroids and no neutropenia. The fever and breathlessness gradually subsided followed by the cough. The patient showed clinical improvement on steroids, which was followed by radiological resolution. A repeat HRCT imaging showed complete resolution of the consolidation and GGOs [figure 2].

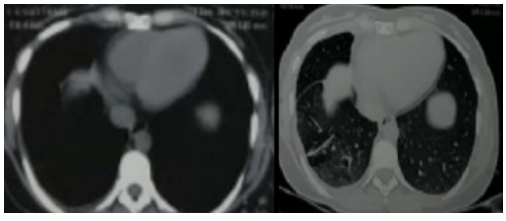

Figure 2: Resolution of pneumonia and concomitant effusion. The patient is symptomatically better with WBC count and platelets within normal range continued on maintenance dose of steroids.

Discussion

Myelodysplastic syndrome [MDS] is a heterogeneous group of hematological disorders that are characterized by abnormal morphology and cytopenias of bone marrow elements[1].

Azacitidine, a ring analogue of the pyrimidine nucleoside cytidine, is

used in the treatment of MDS and produces its cytotoxic effect by interfering with nucleic acid metabolism, and causes hypomethylation of DNA by inhibiting DNA methyltransferase. It undergoes phosphorylation to azacitidine triphosphate, which is incorporated into the ribonucleic acid [RNA], disrupting its metabolism and protein synthesis[1].

In patients with MDS, hypermethylation of DNA is associated with bone marrow proliferation and progression to acute myelogenous leukemia. Hypomethylation of this DNA by azacitidine may also restore the function of genes that control cell proliferation and differentiation[2,3].

Prior to the introduction of hypomethylating agents, including azacitidine, as standard therapies for MDS, cytotoxic medications were the main stay of treatment. However, outcomes following these cytotoxic agents were disappointing[1].

Azacitidine prolongs the survival of patients with MDS as proved by Silverman and co-workers, who reported that the median time to leukemic transformation or death in MDS patients was 21 months with azacitidine and 13 months with supportive care[4].

It has been associated with various adverse reactions including nausea, pyrexia, diarrhoea, fatigue, cough, dyspnoea, and bone marrow suppression which might result in febrile neutropenia, bleeding, and anaemia. Interstitial pneumonitis is probably a rare adverse reaction secondary to azacitidine[1].

Cryptogenic organizing pneumonia [COP], a type of interstitial pneumonitis, affects distal bronchioles, alveolar ducts, and alveoli. Although the pathogenesis is not fully understood, injury to alveolar epithelial cells with imbalance between the activity of matrix metalloproteinase and its inhibitors seem to trigger COP. This leads to leakage of intracellular proteins causing an inflammatory reaction with recruitment of inflammatory cells[5,6].

There are three main characteristic imaging patterns of COP that have been described. These comprise multiple alveolar opacities [typical COP], solitary opacity [focal COP], and infiltrative opacities [infiltrative COP][7].

Pleural effusion as a radiological manifestation with a solitary lesion in the lung parenchyma is rarely seen in COP, although it has been described in a previous retrospective review of COP cases[8].

A diagnosis of drug-induced lung disease is a diagnosis of exclusion and requires the following conditions[7]:

a. drug exposure,
b. exclusion of aetiology of other lung diseases besides a drug reaction,
c. clinical suspicion, radiological findings and pathological patterns that are consistent with those observed with use of the drug,
d. improvement of signs and symptoms following discontinuation of the suspected drug and
e. recurrence of the disease on re-challenge with the drug.

Azacitidine-induced pneumonitis has been described to produce fever, dry cough, breathlessness and radiologic characteristics that appear to be those of eosinophilic pneumonia [EP] or COP[10-15].

Azacitidine was stopped as there was no improvement in the blood counts and we did not re-administer azacitidine because an adverse drug reaction [in the form of the COP] was suspected and it could have been life-threatening if it had been the cause of the lung injury and exacerbated it. In a resource-limited setting like ours, a presumptive diagnosis is enough to warrant extreme caution towards retrying.

Steroids as part of immunotherapy for management of MDS have been proved to help the refractory thrombocytopenia in patients categorized as "low risk"[16]. As our patient had failed to respond to decitabine and had a suspected adverse drug reaction with declining blood counts, steroid therapy was initiated.

The fact that there was radiological and constitutional resolution after stopping azacitidine along with concomitant pulse steroid therapy points towards the likelihood of a drug induced injury.

According to the Naranjo adverse drug reaction probability scale[17], which is used to estimate the probability of an adverse drug reaction, the probability of the lung injury being due to azacitidine was "probable". Hence, we considered our patient's lung disease to be azacitidine induced pneumonitis.

The clinical presentation of azacitidine-induced pneumonitis is very similar to that of neutropenic fever, and sometimes also has radiological and pathological similarity to the interstitial pneumonia associated with MDS.

In our patient, as all blood, sputum and pleural fluid culture reports for infectious etiology were negative, and as the symptoms resolved following stoppage of azacitidine and continuing steroids, a probable etiology could be mentioned as azacitdine induced lung injury.

Thus the causes of lung disease other than azacitidine-induced pneumonitis, such as MDS itself, should be excluded prior to calling the pneumonia as drug induced.

Though rare, we conclude that there is a recognizable potentially life-threatening toxicity due to organizing pneumonia secondary to azacitidine in the setting of MDS treatment.

Conclusion

The clinical presentation of azacitidine-induced pneumonitis is very difficult to diagnose due to its similarity to that of neutropenic fever, and sometimes also has radiological and pathological similarity to the interstitial pneumonia associated with MDS. To pinpoint the exact cause, a microbiological or tissue diagnosis is essential. Drug induced pneumonitis has a potential to be reversed if diagnosed in time and hence needs to be kept in mind while treating patients of MDS.

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