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Occurrence of Bronchiolitis Obliterans Organizing Pneumonia with the Use of Temozolomide Chemotherapy: A Case Report

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Abstract Bronchiolitis Obliterans Organizing Pneumonia (BOOP), also known as Cryptogenic Organizing Pneumonia, is an uncommon disease defined as an inflammation of the bronchioles which resembles pneumonia on imaging but it is in fact non-infectious pneumonia. BOOP associated with Temozolomide has been observed in a few patients and documented very little, hence, internists and oncologists at the frontier of care must be aware of this lung damage. Here we present a case of a 67-year-old patient who presents with bronchiolitis obliterans organizing pneumonia after receiving chemotherapy for Glioblastoma Multiforme with Temozolomide. When discovering the trigger for the illness was Temozolomide, it was promptly discontinued, and treatment with methylprednisolone was promptly initiated, which provided significant improvement.

Keywords: *Bronchiolitis Obliterans Organizing Pneumonia (BOOP), cryptogenic organizing pneumonia, non-infectious pneumonia, Temozolomide, Glioblastoma Multiforme*

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1. Introduction

Bronchiolitis Obliterans Organizing Pneumonia (BOOP) is an uncommon disease defined as an inflammation of the bronchioles which resembles pneumonia on imaging but it is in fact non-infectious pneumonia. Bronchiolitis Obliterans Organizing Pneumonia associated with Temozolomide has been observed in very few patients and is very rarely documented. Temozolomide is an alkylating agent that is hydrolyzed into the metabolite methyl-triazeno-imidazole-carboxamide (MTIC) which methylates guanine-rich areas on DNA and cellular division [1]. The formation of O6-methylguanine through this methylation is the main cytotoxic agent that crosses the blood-brain barrier in excellent concentrations in order to largely treat malignant brain tumors like glioblastoma multiforme and anaplastic astrocytomas [2]. Many a time, patients with BOOP present with flu-like illness with no underlying source of infection. The patient's imaging will present as pneumonia but once antibiotics are initiated patients show no signs of illness regression. Bronchiolitis Obliterans Organizing Pneumonia is an inflammatory reaction in the lung that is reversible by the cessation of the offending agent and prompt initiation of steroids.

2. Case Presentation

A 67-year-old male patient was brought into the hospital for altered mental status with a past medical history of Hypertension and Hyperlipidemia. The patient's daughter provided insight that his symptoms had started a couple of months ago. Initially, she noticed varying personality changes, confusion, and aphasia. An MRI was then ordered, which showed a left frontal lobe mass which led to a diagnosis of Glioblastoma Multiforme. Surgery, Neurology, and Oncology departments were consulted and 2 days post-admission, the patient underwent a stereotactic guided craniotomy with partial resection of the tumor. A combination of Radiation and Chemotherapy was planned. Radiation treatment with Gamma Knife Radiosurgery was initiated on post-op Day 12 days and chemotherapy with Temozolomide 300mg per oral once daily was started on post-op Day 17.

On the night of post-op day 18, the patient developed sudden shortness of breath at which point a stat Chest Xray and Arterial Blood Gas (ABG) was ordered, and the patient was placed on Ventimask with 4L of oxygen. On Physical Exam, the patient's vitals were: temperature of 98.2 F, respiratory rate of 25 breaths/min, blood pressure 128/71 mmHg, and pulse of 106 beats/min. His Oxygen

saturation went from 88 to 96 on a Ventimask at 4L. Auscultation of the lungs showed clear lung fields without any crackles or rales. A cardiology exam of the patient displayed tachycardia with regular S1 and S2. On his first ABG (Table 1) post-op Day 18, the patient presented with a pH of 7.49, CO_2 32, PO_2 50, SO_2 87 HCO_3 28, Aa gradient 48.7; expected Aa gradient 20.8. CXR (Figure 1) that day showed, "Interval development of a bilateral increase in pulmonary hila and increase interstitial with peri bronchial cuffing", which were suggestive findings of pulmonary edema. The next morning post-op Day 19, a repeat ABG (Table 1) showed pH 7.49, CO_2 30, PO_2 63, SO_2 93.2, HCO 22, FiO_2: 40, Aa gradient 184.7; expected Aa gradient 20.8, PaO_2/FiO_2: 157.5.

Table 1. Post-Op ABG Values of the patient

ABG	Post-op Day 18	Post-op Day 19	Post-op Day 20	Refence Range
pH	7.49	7.49	7.54	7.35-7.45
$PaCO_2$	32	30	34	35-45 mm Hg
PaO_2	50	63	72	80-100 mm Hg
SO_2	87	93.2	94	≥ 95%
HCO_3	28	22	23	21-27 mEq/L
A-a Gradient	48.7	184.7	170.7	Normal Range: 10-15 mm Hg / Expected in this Patient: 20.8 mm Hg

Post-Op: Post Operative; ABG: Arterial Blood Gas; pH: acidity; $PaCO_2$: Partial pressure of Carbon dioxide; PO_2: Partial pressure of Oxygen; HCO_3: Bicarbonate; SO_2: Oxygen Saturation; A-a Gradient: alveolar-arterial gradient; mm Hg: millimeters mercury; mEq/L: milliequivalents per Liter.

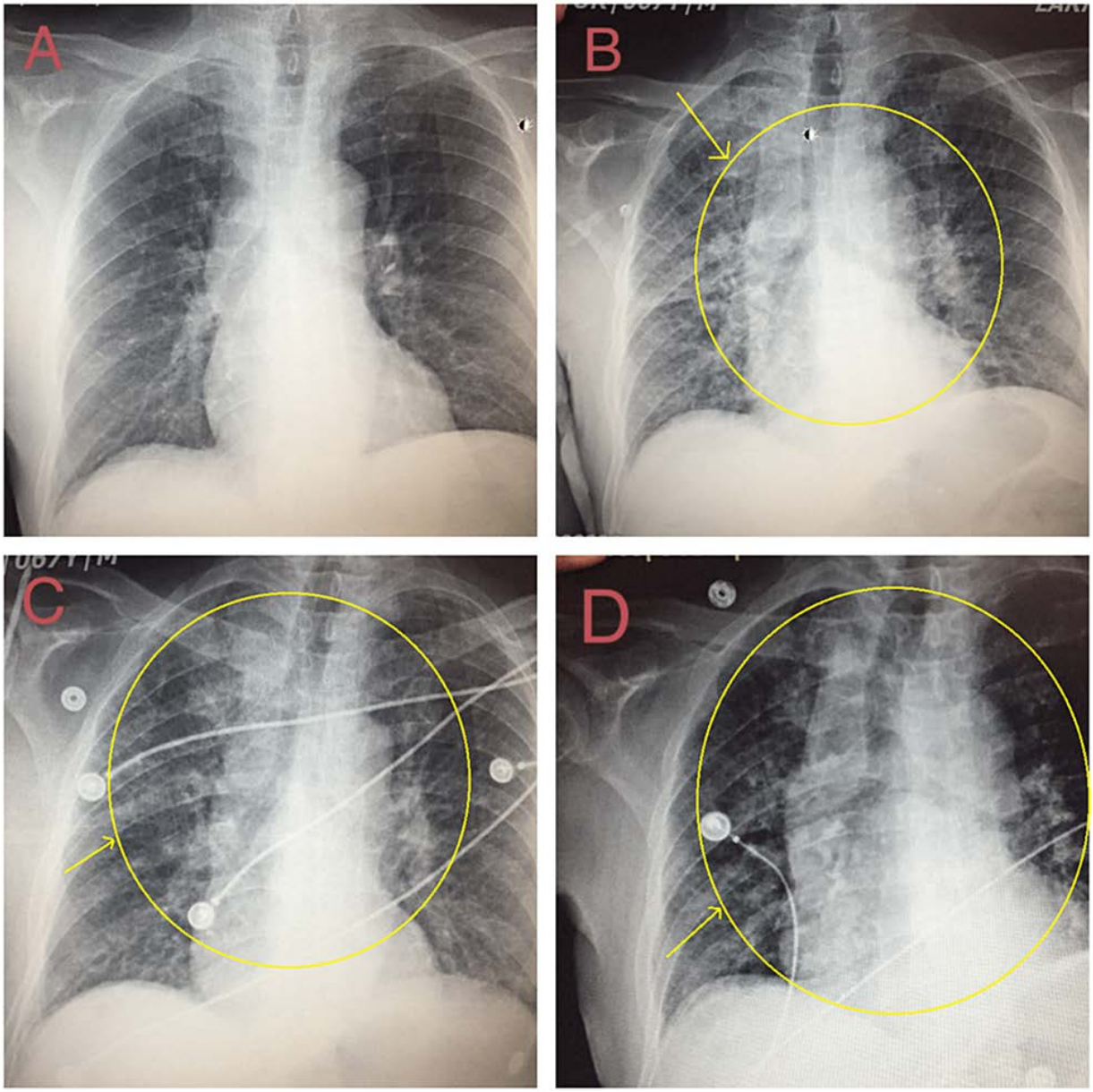

Figure 1. A: Day of Admission. B: On Day 2 of Temozolomide and CXR findings suggested Pulmonary Edema due to an increase in pulmonary hila and an increase in interstitium with peri-bronchial cuffing. C: On Day 1 of terminating Temozolomide, and initiating treatment with methylprednisolone and, CXR showed evidence of Chronic Bronchitis. D: On day 3 of methylprednisolone and stopping Temozolomide, CXR showed an inflammatory process with underlying chronic interstitial changes

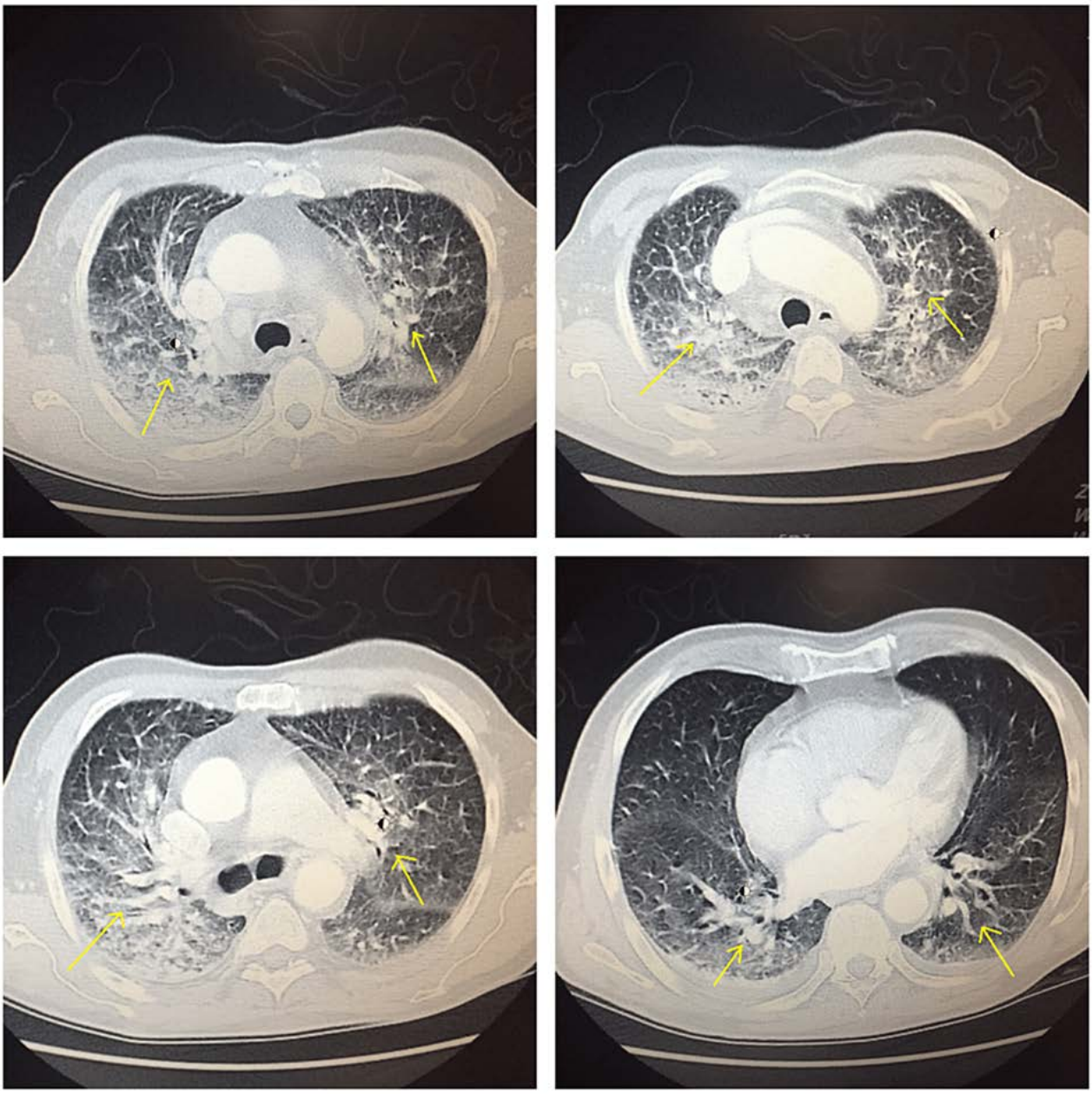

Figure 2. CT Chest with Contrast: Diffuse bronchiolectasis. Diffuse patchy consolidation predominantly subpleural and peribronchial in distribution. Bronchial wall thickening. These findings are consistent with cryptogenic organizing pneumonia

2.1. CXR: Chest X-Ray

A CT (Figure 2) scan showed a Diffuse patchy consolidation predominantly subpleural and peribronchial in distribution and bronchial wall thickening. These findings are consistent with cryptogenic organizing pneumonia but because of the patient's WBC count of 9.6 thou/uL, and Temperature was 98.2 F; we considered it an unlikely cause at that time. The patient was started on Piperacillin/Tazobactam 3.375gm every 8 hours empirically, but despite the medication, the patient developed respiratory distress the following night.

2.2. CT: Computed Tomography

The patient's decline in clinical status prompted us to conduct a bronchoscopy with bronchoalveolar lavage and characteristic morphological and histological findings lead to a suspicion of Bronchiolitis Obliterans Organizing Pneumonia as a working diagnosis of the patient's symptoms. With further research and the duration of the development of BOOP, we suspected drug-associated BOOP as the preliminary etiology. Antineoplastic agent temozolomide had been reported as a rare cause of bronchiolitis obliterans organizing pneumonia, hence, temozolomide therapy was immediately terminated. We additionally provided a conventional dose of Methylprednisolone at 1mg/kg/day to the patient for symptomatic relief. After the patient received 125mg of methylprednisolone, an ABG sample was repeated. The results were as follows: ABG (Table 1) post-op Day 20: Ph 7.45, PCO2 34, PO2 72, HCO3 23, SO2 94. FiO2 40, Aa gradient 170.7; expected Aa gradient 20.8 PaO2/FiO2: 180. The patient showed a rapid response and significant improvement in his respiratory status following treatment management. We then concluded **Temozolomide-associated BOOP** as the definitive diagnosis for this patient's respiratory symptoms.

3. Discussion

Alkylating agents and their metabolites act nonspecifically and affect both cancerous and normal cells alike. The pathogenesis of Bronchiolitis Obliterans Organizing Pneumonia in this case is that of an inflammatory process caused by Temozolomide, rather than fibrosing lung disease. Patients with BOOP usually present with flu-like symptoms who undergo antibiotic therapy [1], but after no resolution of symptoms, providers must look at noninfectious causes of pulmonary damage. Temozolomide as an alkylating agent also has potential side effects that physicians must be mindful of such as lymphopenia, thrombocytopenia, interstitial pneumonitis, pulmonary fibrosis, and hepatotoxicity; to name a few [3]. Hence with that consideration, Temozolomide should be used cautiously as it is a very effective agent in treating many central tumors due to it being orally absorbed and its metabolites having the ability to cross the blood-brain barrier, but also causing rare inflammatory reactions [4].

Other case reports show patients that present with pulmonary symptoms within two weeks of starting treatment. We attribute the early onset of our patient's symptoms primarily due to our patient being an inpatient in the hospital with constant monitoring. At the time of the patient's presentation, we were worried about Pulmonary Embolism vs BOOP vs Pulmonary Edema.

The patient had risk factors for Pulmonary Embolism such as cancer like Glioblastoma Multiforme (GBM) with a very high hypercoagulable state: Upper extremity Deep Venous Thrombosis (DVT), Lower extremity DVT, and the patient was unable to receive anticoagulation due to his recent brain surgery. Therefore, an Inferior Vena Cava Filter (IVCF) was placed on post-op Day 18. The patient had an O2 saturation of 94-97 on ventimask with oxygen so we suspected that pulmonary embolism was unlikely at this time, but due to the sudden onset of shortness of breath and his risk factors, this was a diagnosis that needed to be ruled out before we could move further with our workup.

The radiology report stated Pulmonary Edema was seen on the stat CXR but on physical exam patient had no crackles or rales heard on the lung exam. The lungs were clear to auscultation bilaterally with diminished breath sounds on lower lung fields, that were secondary to the patient refusing to take full deep breaths. The patient could have pulmonary edema secondary to hyponatremia and low serum osmolality but that was very unlikely at that point. With the patient being asymptomatic in the days leading to the shortness of breath episode, a possible differential was flash pulmonary edema. Flash pulmonary edema or cardiogenic alveolar pulmonary edema was very unlikely for this patient as he had no cardiac history such as heart failure or risk for myocardial infarctions at the time [5].

BOOP, also known as Cryptogenic Organizing Pneumonia is a fairly uncommon disease that presents symptomatically as an infection. Symptoms usually consist of shortness of breath, dyspnea, fatigue, and elevated temperature [6]. The patient's physical exam of the lungs is usually unremarkable without any crackles, wheezing or rales appreciated.

Studies suggest, that the combination of cytological bronchoalveolar lavage and histological transbronchial lung biopsy data obtained during a fibreoptic procedure is an effective method for the initial investigation of BOOP which presents with patchy radiographic shadows [7]. BOOP can be diagnosed through a transbronchial biopsy of a small amount of lung tissue, or a wedge biopsy from at-least 2 lobes of the lung. [8]. A high-resolution CT scan (HRCT), with bronchoalveolar lavage, is less invasive and may also be considered another alternative used. On a biopsy of the lung tissue, you expect to see fibroblastic plugs in the bronchial lumen with spindled fibroblasts in a matrix with immature loose collagen. On a HRCT patients show ground glass opacity with a peri-bronchial distribution of consolidation. 71% of patients present with bronchial wall thickening in air bronchograms with cylindrical bronchial dilatation.

The mainstay of treatment of BOOP starts with stopping the insulting agent and patients may show resolution of the symptoms within days to weeks. Patients usually require treatment with corticosteroids [9]. The recommended dose is 0.75mg/kg/day for 1 to 3 months depending on the severity of the insult. Tapering of the steroids begins at 3 months; the dose is reduced to 0.5mg/kg/day for another 3 months before another taper happens. Patients are then tapered to a dose of 10 to 20 mg/day for another 12 months [10]. Approximately one-third of all patients with BOOP treated for less than a year have disease relapse and are required to be put back on steroids to achieve resolution [11], but do not affect long-term outcomes in terms of morbidity or mortality [8].

4. Conclusions

This case was of a patient receiving Temozolomide chemotherapy for Glioblastoma Multiforme. After several days of treatment, the patient developed shortness of breath and oxygen desaturation. The patient was then worked up for pulmonary embolism due to his risk factors vs pulmonary edema vs pneumonia as seen on CXR. After extensive workup through various radiographic findings, lab results, and physical exam findings, we were able to rule out these suspected differentials. With the discontinuation of Temozolomide and initiation of methylprednisolone initially with 125 mg, followed by 80mg IV Daily, the patient started showing significant improvement. This significant symptomatic improvement of the patient's respiratory status with discontinuation of Temozolomide verified the non-infectious definitive diagnosis of Temozolomide-associated Bronchiolitis Obliterans Organizing Pneumonia.

Abbreviations

MTIC: methyl-triazeno-imidazole-carboxamide; ABG: Arterial Blood Gas; CXR: Chest X-Ray; CT: Computed Tomography; HRCT: high-resolution CT scan; GBM: Glioblastoma Multiforme; DVT: Deep Venous Thrombosis; IVCF: Inferior Vena Cava Filter; Post-Op: Post Operative; ABG: Arterial Blood Gas; pH: acidity;

$PaCO_2$: Partial pressure of Carbon dioxide; PO_2: Partial pressure of Oxygen; HCO_3: Bicarbonate; SO_2: Oxygen Saturation; A-a Gradient: alveolar-arterial gradient.

Authors' Contributions

All authors participated in the management of this patient, conceived the idea of the case report, and participated in the drafting of the study.

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Competing Interests

All authors in this case report declare that they have no competing interests.

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