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Methylprednisolone Resistant Bronchiolitis Obliterans Organizing Pneumonia - Treated Successfully with Cyclosporin

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Bronchiolitis obliterans organizing pneumonia (BOOP) usually has an indolent course and a good prognosis, but it may rapidly worsen and respiratory failure may develop; in this situation it should be treated aggressively with a combination of intravenous high-dose corticosteroids and immunosuppressants. We present a case of BOOP with fulminant respiratory failure, which was unresponsive to conventional medical therapy and methylprednisolone, but was treated successfully with the addition of cyclosporin.

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Bronchiolitis obliterans is a term applied to widespread inflammatory and fibrotic obstruction of small airways[1,2]. Initially this syndrome was thought to be restricted to those patients who had suffered severe, viral infections in childhood, particularly those due to parainfluenza virus. However, recently this syndrome has been described in adult patients with rheumatoid arthritis[3]. The response to bronchodilator treatment is poor, as would be expected from the histopathologic findings and fatal respiratory failure which often ensues within two years. There have been reports suggesting a relationship between penicillamine therapy and the development of bronchiolitis obliterans in patients with rheumatoid arthritis. However, this syndrome can develop in patients who have never received penicillamine. This syndrome with similar histopathology has been described in recipients of autologous bone marrow transplants[4]. Although most often interstitial pneumonitis and fibrosis are sequelae, it has been documented that some patients develop a bronchiolitis obliterans picture. It appears that the development of this process occurs most often in the setting of a chronic graft-versus-host syndrome. However, it is clear that diffuse airways obstruction has developed without evidence of this syndrome in bone marrow recipients[3,4].

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THE CASE

The patient was 40 years old Bahraini female, who presented with a history of dyspnoea and dry cough of three weeks duration without any previous history of medical illness. Her history revealed that she had progressively developed dyspnoea on exertion over the past three weeks. Two-dimensional echocardiography gave normal study but chest radiographs showed bilateral infiltrates, more marked on the right side, for which she received a course of antibiotic therapy without response Figure 1.

Figure 1. Initial chest radiograph showing bilateral infiltrates, more marked on the right side.

On initial examination in the Accident and Emergency department, she was found to be dyspnoeic and cyanosed. Other findings revealed her heart rate to be 102 beats/minute, her respiratory rate was 38 breaths/minute, saturation by pulse oximetry was 88%. She had blood pressure of 142/66 mmHg and normal body temperature. Examination of her respiratory system revealed dullness to percussion on both sides, more prominent on the right side; crepitations were present in both infrascapular regions but again more marked in the right infrascapular region. Arterial blood gases at room air were pH 7.16, $PaCO_2$ 29.4 mmHg, PaO_2 56.4 mmHg and an oxygen saturation of 84%. The provisional diagnoses included bronchopneumonia, pulmonary thromboembolism and cardiac dysfunction, but her lung ventilation/perfusion scan was of low probability. Transesophageal echocardiography (TEE), Doppler study and ECG for cardiac dysfunction were normal. She was prescribed Erythromycin 500mg qid along with Salbutamol and Ipratropium nebulization, but she did not respond to this treatment and was transferred to the Intensive Care Unit (ICU).

Along with Erythromycin, Ceftriaxone 2gms/day was added as atypical pneumonia was considered the most likely diagnosis. Supportive treatment continued in the form of nebulization, inspired air humidification and chest physiotherapy. The patient responded to treatment and was transferred from the ICU to the medical ward, where her condition deteriorated after three days. She developed fever and became tachypneic and drowsy; BP 84/60 mmHg, MAP 49 mmHg, heart rate of 126 beats/minute, arterial blood gases of pH 7.15, $PaCO_2$ 62 mmHg, PaO_2 51 mmHg, saturation 81% at 10 Litres/minute oxygen by face mask. She was intubated and again transferred to the ICU. In the ICU she was maintained with pressure-controlled ventilation under sedation and muscle relaxant (FiO_2 1.0 Litre/minute, PEEP 15 mmHg, RR 24/minute, TV 350 mL and PIP 20 mmHg). Her ABG on these settings was pH 7.21, $PaCO_2$ 43 mmHg, and PaO_2 66 mmHg, with saturation 92%. She was drowsy and her blood pressure remained 90/60 mmHg with inotropic support. Ventilatory settings were adjusted to keep her PaO_2 more than 60 mmHg but she continued to deteriorate. She was then placed on Piperacillin and Tazobactam along with Vancomycin.

A bronchoscopy was performed but was not helpful in making a diagnosis as the broncho-alveolar lavage fluid was sterile. Bilateral open lung biopsy was performed and an

intercostal drain (ICD) inserted. The histopathology showed interstitial pneumonia and thickened fibrosed hyalinized collapsed alveoli filled with macrophages, and alveolar septal inflammation with fibrotic honeycombing, and one vessel filled with thrombus. Based on histopathology, the diagnosis of bronchiolitis obliterans organizing pneumonia (BOOP) was made Figure 2.

Figure 2. Characteristic fibroblastic plugs -"Masson's bodies" filling alveoli with some thickening of alveolar septa. Haematoxylin and Eosin, x 160.

Methylprednisolone was added to the treatment and protective lung strategies (endotracheal intubation with a cuffed tube) with permissible hypercapnia were begun for ventilatory therapy but her condition continued to deteriorate. After 15 days of Methylprednisolone therapy, Cyclosporin 400mg/day was added, after four days the patient started to show a favorable response in the form of improved arterial oxygen (ABG pH 7.36, $PaCO_2$ 70 mmHg, PaO_2 66 mmHg at a FiO_2 of 0.5). Over the following two weeks, she was successfully weaned from the ventilator and was transferred from the ICU to the medical ward. Later she was discharged from the hospital.

DISCUSSION

Bronchiolitis obliterans organizing pneumonia (BOOP) is a clinicopathological syndrome associated with a variety of disease entities[5]. The most frequent presenting symptoms are cough and dyspnoea. Bilateral multifocal consolidation along with alveolar infiltrates predominantly in the lower lobes, which are migratory in nature, is another common radiological finding but for confirmation of diagnosis, histopathology is required. Transbronchial biopsy is diagnostic in most cases but open lung biopsy is needed in doubtful cases[6]. Response to medical therapy is good but in rapidly progressing BOOP the clinical outcome is poor. The Corticosteroids and Cyclosporin have been tried alone or in combinations with variable success[7]. Inhalation Triamcinolone also has been used successfully in case of BOOP, where oral and systemic steroid therapy was not acceptable to the patient[8].

Numerous aetiologies have recently been described for this infrequently encountered clinical condition that can mimic a number of pathologic lung processes. A recent retrospective study of patients with an underlying diagnosis of cancer showed a treatable cause of lung disease with variable manifestations. This group showed that BOOP can mimic pulmonary malignancy and pulmonary infection[9]. Some case reports have described the association of immunocompetent adults. Bone marrow transplant patients who are immunosuppressed have exhibited BOOP symptoms which makes the diagnosis of the syndrome very complicated[10-13]. Other isolated case reports have shown unusual occurrences of BOOP syndrome in patients with radiation pneumonitis or various dermatological diseases, and in antiphospholipid (Hughes syndrome) patients[14-17]. A thorough literature search did reveal a

minimal number of cases in which patients similar to ours underwent successful treatment of idiopathic BOOP with simultaneous administration of Cyclosporin 'A' and corticosteroids which elicited rapid improvement[3,17,18].

The clinical presentation of our case was a dry cough and dyspnoea on exertion. Clinical suspicion included underlying cardiac pathology for which ECG, 2D echo and TEE were done. All proved to be normal. Bilateral diffuse radio-opaque infiltrates prompted the provisional diagnosis of atypical pneumonia and/or pulmonary thromboembolism, but a ventilation/perfusion scan was in the low probability group.

Considering the diagnosis of atypical pneumonia, she was initially treated with Erythromycin and Ceftriaxone. She deteriorated further and was unresponsive to the antibiotic therapy. Bronchoscopy had not been helpful in making a diagnosis because the broncho-alveolar lavage fluid was sterile. Bilateral open lung biopsy was performed to reach the final diagnosis of BOOP.

CONCLUSION

Because BOOP is rare clinical entity in our part of world, the diagnosis was delayed and appropriate treatment was started only after the biopsy report. Based on our experience with this case, we suggest that patients with a long-standing nonproductive cough and dyspnoea, unresponsive to antibiotic therapy and sterile bronchoalveolar lavage, an early open lung biopsy should be considered. If the patient is resistant to steroid therapy, Cyclosporin should be added to the treatment without further delay.

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