INTRODUCTION

Bronchiolitis obliterans organizing pneumonia (BOOP) is an inflammatory condition of the lung which has been found to be associated with a variety of medical conditions. But till date, no direct association of BOOP with multiple myeloma has been elucidated. We describe a patient who was diagnosed to have BOOP coexisting with multiple myeloma. Recurrent respiratory infections due to suppressed immunity in multiple myeloma may be an inciting cause. As of now, more cases are required to substantiate our hypothesis.

CASE REPORT

A 70 years old non-diabetic non-hypertensive patient from sub-urban Kolkata, India, presented with drowsiness followed by altered sensorium for the last 4-5 days. He had been suffering from occasional fever for the last 2 months with dry cough but without any history of expectoration nausea, vomiting or headache. Various investigations had been done outside including a chest X-ray (CXR) and computerized tomography (CT) scan of thorax that pointed to a diagnosis of bronchiolitis obliterans organizing pneumonia (BOOP) [Figures 1-3]. On admission, clinical examination revealed a Glasgow coma scale of 6/15. There was the presence of a moderate pallor in the general survey. There were mild crepitations bilaterally throughout the chest wall, and Kernig's sign and neck rigidity were found to be positive. Other than these, there were no abnormalities on systemic examination.

Routine investigations including complete blood count and electrolytes showed total leucocyte count 11000/cmm (neutrophils 88, lymphocytes 10, eosinophils 1 and monocytes 1%) and platelets 32000/cmm. Peripheral blood picture was suggestive of normocytic normochromic anemia: Hemoglobin 7.3 g/dl, mean corpuscular volume 106.1 fl, mean corpuscular hemoglobin (MCH) 32.1 pg, mean corpuscular hemoglobin concentration (MCHC) 30.3. Erythrocyte sedimentation rate (ESR) was raised (102 mm after 1st h). Electrolytes were suggestive of hypomagnesemia (1.52 mmol/l) and hypercalcemia (13.2 mmol/l). Potassium and magnesium were normal. Albumin was decreased, but globulin raised.

Brain CT scan showed diffuse cerebral edema with mild cortical atrophy. Cerebrospinal fluid (CSF) report showed a cell count of 50/cmm (neutrophils 80 and lymphocytes 20%).
glucose 36 mg/dl, protein 78 mg/dl, and adenosine deaminase activity (ADA) 0.6 U/l suggestive of bacterial meningitis. CSF culture was positive for *Meningococcus*, which was sensitive to ceftriaxone.

Plasma urea 72 mg/dl, creatinine 2.4 mg/dl, repeated sample of Ca²⁺ 13.2 mmol/l suggestive of hypercalcemia; 1, 25(OH) vitamin D was within normal limits. Ultrasonography kidneys-ureters-bladder region showed bilaterally reduced kidney size. Serum iron was 47.8 ng/dl, total iron binding capacity 161.6 ng/dl and ferritin 812 μg/l indicating an anemia of chronic disease. X-ray of the skull, humerus and chest [Figures 4-6] showed multiple lytic bony lesions.

Urinary Bence Jones protein was negative, but serum β₂-microglobulin was raised (3.5 g/dl) [Figure 7]. Both serum and urine protein electrophoresis showed characteristic ‘M’ spike in gamma globulin region. Sputum for acid fast bacilli was negative twice. HIV I/II, HBsAg, anti-HCV and Mantoux test all were negative. Sputum culture was also negative. A transbronchial biopsy was done after stabilizing the patient, which gave us a picture suggestive of BOOP [Figure 7]. A bone marrow biopsy following an inconclusive bone marrow aspiration was done showing only 6% of plasma cells along with decreased myelopoiesis and megakaryopoiesis.

Based on these reports, a diagnosis of possible multiple myeloma (MM) with related organ and tissue injury, as manifested by hypercalcemia, anemia, kidney disease and lytic bone lesions, complicated by BOOP and bacterial meningoencephalitis was made.
The patient was treated conservatively with intravenous (IV) ceftriaxone and dexamethasone along with other supportive management. He was also given a single dose of zoledronate for hypercalcemia of malignancy. Since meningoencephalitis is a medical emergency, the bone biopsy could only be done after stabilization of the patient with steroids and antibiotics, which can explain the reduced plasma cell population in the bone marrow of the patient. The patient was discharged on request after 1 month of hospital stay as he was unwilling to stay in the hospital anymore.

After 2 months, the patient was admitted again with similar presentation of lethargy and drowsiness but there was no fever. Again blood parameters were suggestive of hypercalcemia. Repeat CSF was unremarkable. Again bone marrow biopsy was done, which showed increased plasma cell count in bone marrow (26%) suggestive of MM. The patient received IV methylprednisolone and melphalan as he could not afford bortezomib and lenalidomide and was discharged in a stable condition with suggestions of follow-up. His respiratory symptoms have also been decreased during this time [Table 1].

**DISCUSSION**

Among the large group of monoclonal gammopathies, MM is a very common disease. It is a malignant proliferation of plasma cells derived from a single clone presenting with

<table>
<thead>
<tr>
<th>Period</th>
<th>Presenting features</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>December 2013</td>
<td>Dry cough f/b fever and altered sensorium</td>
<td>Diagnosed as BOOP with meningoencephalitis and hypercalcemia probably due to multiple myeloma with ROTI; discharged on request after stabilization</td>
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<tr>
<td>March 2014</td>
<td>Lethargy and drowsiness</td>
<td>Hypercalcemia due to multiple myeloma; discharged after giving first cycle of melphalan and methylprednisolone</td>
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BOOP: Bronchiolitis obliterans organizing pneumonia, ROTI: Related organ and tissue injury

**Table 1: Mode of presentation of the patient in a chronological order**
different symptoms including bone pain or pathological fracture, susceptibility to infections, renal insufficiency and various neurological symptoms, anemia, hypercalcemia, clotting abnormalities etc. Though the cause is unknown, exposure to radiation, a variety of chromosomal alteration can be the underlying cause. Median age of diagnosis is 70 years and affects males more commonly than females.

The Diagnostic Criteria for MM

All of the following three criteria must be met [1]:

1. Clonal bone marrow plasma cells ≥10% or biopsy-proven plasmacytoma
2. Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma)
3. Evidence of end organ damage that can be attributed to the underlying plasma-cell proliferative disorder, specifically characterized by (a) hypercalcemia (serum calcium ≥ 11.5 mg/dl or (b) renal insufficiency (serum creatinine > 173 mmol/l or 2 mg/dl or estimated creatinine clearance <40 ml/min), (c) anemia (normochromic, normocytic with a hemoglobin value of > 2 g/dl below the lower limit of normal or a hemoglobin value of <10 g/dl, and (d) bone lesions (lytic lesions, severe osteopenia or pathologic fractures) [2].

In this case, the patient had (1) presence of M spike (monoclonal spike) both in serum and urinary electrophoresis, (2) hypercalcemia, normocytic normochromic anemia, creatinine > 2 g/dl or creatinine clearance of approx. 23 ml/min and multiple bony lytic lesions on skull, chest and humerus, and (3) though initially the plasma cells were ~6% on bone marrow biopsy, repeat bone marrow biopsy showed ~26% plasma cells in bone marrow, thus fulfilling all three criteria of MM. Though the patient presented with a bacterial meningococcalitis prior to admission, the patient was already suffering from dry, nonproductive cough associated with fever, which was diagnosed as BOOP for 2 months.

BOOP is a noninfectious inflammation of bronchioles and surrounding tissue but different from other pulmonary inflammatory disorders such as chronic obstructive pulmonary disease, asthma and granulomatous lung disease [3]. Presence of granulosis tissue within bronchiolar lumen and alveolar ducts (not in distal air spaces) associated with a variable degree of interstitial and airspace infiltration by mononuclear cells and foamy macrophages are characteristic of BOOP [4,5]. It can be grossly divided into 2 types: Primary or idiopathic, in which the cause is not known; and secondary, generally to some systemic disease [6].

In most cases, symptoms include persistent nonproductive cough, effort dyspnea, low-grade pyrexia, malaise and weight loss and often preceded by a flu-like illness. Fine, dry lung crepitations on auscultation, absence of clubbing, raised ESR and usually a restrictive pattern in pulmonary function test along with bilateral patchy opacities in CXR and characteristic finding in high-resolution CT should point toward the diagnosis of BOOP. Definitive diagnosis is by tissue examination by open lung or transbronchial biopsy [7]. Differential diagnosis of BOOP should include collagen vascular disease, lung metastases, infective pneumonias, Wegener granulomatosis, eosinophilic pneumonia, primary bronchogenic neoplasm and tuberculosis [8].

BOOP has been reported in association with almost all connective tissue disorders, organ transplantation, especially with bone marrow transplant recipients. Cytomegalovirus pneumonia-associated BOOP has been reported following lung transplantation, which usually responds quickly to corticosteroids [9]. BOOP following renal transplantation has been described in only one patient, which responded quickly with an increase in dose of corticosteroids. Radiotherapy associated BOOP usually occurs in patients receiving radiotherapy for breast carcinoma [10].

It is associated with a variety of unrelated conditions like: Essential mixed cryoglobulinemia, myelodysplastic syndrome, interstitial cystitis, chronic thyroiditis, sarcoidosis, alcoholic cirrhosis and a seasonal syndrome with cholestasis in England [11]. Association might be with lymphoma/leukemia and other neoplastic processes also. BOOP has also been reported in primary biliary cirrhosis and after coronary artery bypass graft surgery. Evans syndrome and chronic sinusitis, lung cancer, lung atelectasis, asthma, cystic fibrosis, secondary amyloidosis, Sweet’s syndrome [12], idiopathic thrombocytopenic purpura and Fabry’s disease [13]. BOOP can follow all types of pneumonias when long term symptoms and radiographic changes persist despite an initial improvement in symptoms and signs. Thus, the pneumonic process gradually evolves into BOOP. This distinction is important as these patients usually respond well to corticosteroids.

A variety of drugs has been associated with BOOP [14]. Cases of phenytoin-associated BOOP and carbamazepine-induced lupus erythematosus with concomitant BOOP responded rapidly to corticosteroids. A case of ticlopidine-associated BOOP resolved following the withdrawal of the offending agent. Antibiotics, sulfasalazine, cephalosporin, sulfamethoxypyridazine, amphotericin, acetobutol, sotalol, amiodarone, bleomycin, busulfan, methotrexate, cocaine, gold salts, interferon alpha and tacrolimus are the other drugs, which has been associated with BOOP. Environmental effects like textile printing dye and house fire has also been associated with BOOP.

BOOP may resolve spontaneously; however, corticosteroids are the standard mode of treatment currently [15]. The dosage is generally 0.75 mg/kg/day for 1-3 months, then 0.5 mg/kg/day for 5 months, then 10-20 mg/day or every other day for a total of 1 year. Alternate day drug scheduling can be successfully used for this entity. A shorter 6-month course may be used in certain situations. However, this duration can extend up to 12 months or even longer due to relapses in disease activity and symptoms. A total and permanent recovery is seen in most of the patients, but it is also dependent on the cause or associated systemic disorders. Erythromycin, inhaled triamcinolone, azathioprine, cyclosporin and cyclophosphamide have also been used to treat BOOP [16,17].
Nevertheless, till now no direct association between BOOP with multiple myeloma has been reported which is present in this patient. Recurrent pneumonias resulting from immunodeficiency may be a possible pathophysiologic explanation. Other mechanisms may also be involved, but it is too early to comment at this point. Further cases are needed to formulate a definite concept.

**CONCLUSION**

The primary variety of BOOP is idiopathic whereas the secondary variety has been associated with a large group of systemic disorders. As seen in this patient, it can also be associated with multiple myeloma. Recurrent pneumonia due to deficient immunity may be a possible etiological factor. Whether this association is sporadic or has a genetic or environmental basis remains to be seen. As of now, it is too early to comment on this without any further cases; but we have to be vigilant enough to diagnose BOOP in a case of non-remitting respiratory distress in a case of multiple myeloma.

**REFERENCES**