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Case Report

Acute Diffuse Alveolar Hemorrhage following Intravesical Bacille Calmette-Guérin Immunotherapy for Superficial Bladder Cancer

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Abstract

We report a case of a 80-year-old man who presented to our emergency department for high fever (39°C), hematuria and dyspnea four hours after intravesicaladministration of Calmette-Guérin bacille (BCG) for a superficial bladder cancer. The patient already underwent two cycles of instillation. He developed hypoxemic respiratory failure with diffuse alveolitis at chest CT scan. Leukocyte count was 2.93 x 10^9/L, liver function test revealed aspartate aminotransferase 189U/L (15-37 U/L) and alanine aminotransferase 113 U/L (30-65 U/L). Search for Legionella and pneumococcal urinary antigen and sputum staining for *Mycobacterium Tubercolosis* were negative. A bronchoscopy revealed diffuse alveolar hemorrhage. The analysis of the bronchoalveolar lavage (BAL) fluid was negative for Mycobacterial species, *pneumocystis jirovecii*, and other bacterial and viral infection. The nasopharingeal swab for H1N1 was negative as well as results of galactomannan in serum and BAL. Empiric antibiotic treatment was started with no benefits. There was a rapid and significant clinical and radiological improvement with pulsed bolus of steroids and i.v. Immunoglobulins. A control of the computed tomography of the chest revealed multiple ground-glass opacities on both lung fields. Search for autoantibodies (i.e. ANCA, GBM) turned negative as well as BAL cytology. We supposed that a diagnosis of hypersensitivity interstitial pneumonitis with haemorrhagic alveolitis was the most fitting with the clinical picture. In literature there are few reports on hypersensitivity pneumonitis (HP) following intravesical instillation of BCG and none with haemorrhagic alveolitis. HP is explained by a hypersensitivity phenomenon following, usually, traumatic instillation of BCG. Hypersensitivity pneumonitis (HP) is a rare immunologically mediated lung disease caused by repeated exposition of organic antigens and should be considered in patients with acute respiratory symptoms with onset soon after immunotherapy with BCG.

Keywords: Acute Diffuse Alveolar Hemorrhage; Bacille Calmette-Guérin; Superficial Bladder Cancer; Hypersensitivity Pneumonitis

Introduction

Hypersensitivity pneumonitis (HP) is an immunologically mediated lung disease caused by repeated exposition to organic antigens [1,2]. Among many other and more common etiologies, intravesicaladministration of Bacille Calmette-Guérin (BCG) has been rarely described as a cause of HP [3-6]. Moreover, HP rarely is so grave to cause widespread damage of the alveolocapillary membrane, an anatomical-clinical condition known as diffuse alveolar haemorrhage (DAH). DAH is a very severe syndrome that is burdened by high mortality despite aggressive treatment [7], and nowadays no cases of DAH fol-

lowing intravesical BCG administration have been reported in medical literature. Herein, we report the first case of HP associated with DAH caused by intravesical BCG administration for the treatment of superficial bladder cancer.

Case description

An 80-year-old man presented to the emergency department of the General and University Hospital of Careggi, Florence, for high-grade fever (T 39°C), dyspnea and one episode of hemoptysis.

Symptoms started soon after intravesical instillation of a 6-month maintenance dose of BCG-RIVM derived from seed 1173-P2 from 2 × 10^9 to 3× 10^9 viable units (Marketing authorization Holder and Manufacturer: Medac), administered for high grade T1 bladder cancer. During that procedure a mild traumatic injury through bladder catheter insertion caused hematuria that persisted for several hours thereafter and was complicated 3 hours later with high-grade fever treated empirically with ciprofloxacin. The patient already received two doses apart of the same BCG instillation in the previous 6 months (e.g. the induction dose and the first maintenance dose at 3 months).

His previous medical history was remarkable for hypertension, chronic obstructive pulmonary disease (COPD), non small cell lung cancer treated by surgical lobectomy 4 years earlier and with negative follow-up for recurrence, stable coronary artery disease (CAD) treated with coronary artery by-pass graft and pace-maker insertion 7 years earlier; there was no history of allergy. Usual medications were ramipril 2.5 mg, carvedilol 6.25 mg twice daily, acetylsalicylic acid (ASA) 100 mg, salmeterol xinafoate and fluticasone propionate inhalation powder 25/125 mg twice daily.

On hospital admission (3 days after the procedure) the patient was febrile, eupnoic, with normal hemodynamic parameters. Gross hematuria was present and physical examination of the chest and abdomen was normal. An abdominal ultrasonography showed no pathological findings and a chest x ray showed no pulmonary consolidations. Blood gas parameters were indicative of respiratory failure (pH 7,40, pO_2 53mmHg, pCO_2 47mmHg). Leukocyte count was 2.93 x 10^9/L (neutrophils 74.8%; lymphocytes 9.9%; monocytes 14.3%; eosinophyls 0.3%). Liver function tests showed moderate increase in aspartate aminotransferase 189 U/L (normal values 15-37 U/L) and alanine aminotransferase 113 U/L (normal values 30-65 U/L). Because the presence of hypoxia a thorax CT scan with and without contrast dye was ordered (Figure 1a). On direct imaging there were bilateral diffuse ground-glass opacities and peribronchial alveolar septal thickening predominantly affecting the lower lobes, there were no signs of pulmonary embolism. At echocardiography there were neither signs of right and left ventricular dysfunction, nor valvular abnormalities. At the color-doppler sonography of the lower limbs no signs of deep venous thrombosis (DVT) were detected. For the persistence of fever the patient was hospitalized and admitted to the infectious disease unit of the same hospital with a diagnosis of "sepsis due to post-procedural urinary tract infection". The patient started broad-spectrum antibiotic treatment (imipenem/ cilastatin 500 mg q8hr , vancomycin 1g IV q12hr, azithromycin 500 mg IV, trimethoprim/sulfamethoxazole 240/1200 mg IV q8hr). In the following days respiratory failure persisted with occasional episodes of hemoptysis. Seven days after the admission, because inadequate oxygenation while breathing oxygen at 90% concentration, the patient was transferred to our Intermediate Care Unit (IMC) for advanced respiratory treatment and monitoring.

On the arrival at IMC the patient had severe respiratory distress (PAO/FiO_2=43) with no hemodynamic compromise. A trial of non-invasive mechanical ventilation was initiated. Blood tests were normal, and there were no signs of bacterial infection (leukocyte count was 10,00 X 10^9/L, procalcitonin 0.41). Urinary antigens of Legionella and S. pneumoniae, along with real time polymerase chain reaction for S. pneumoniae were negative. The patient's blood and urine cultures were negative as the Gram and acid-fast bacteria staining of the sputum. Serum immunoglobulins (Ig) G and A were normal, while IgM fraction was increased (6.84 g/L; normal values 0.40-2.30 g/L).

A second chest CT scan (day 8 after admission) (Figure 1b) showed massive diffuse alveolitis with extensive patchy and confluent ground glass opacities in both lung fields. Interlobular septa were also thickened, with areas of consolidation producing images suggesting a "crazy paving" appearance. On the same day after initial respiratory stabilization, while the patient was on noninvasive mechanical ventilation, a fibrobronchoscopy revealed diffuse hemorrhage. Fluids from a bronchoalveolar lavage (BAL) were collected and sent to the laboratory for microbiological analysis. There was no evidence of bleeding in other organs, coagulation tests and platelet count were normal (PLT 254 X 10^9/L, PT 77%, INR 1,2 , aPTT 26.7 sec). The analysis of the BAL fluid was negative for Mycobacterial species, *Pneumocystis jirovecii*, and other bacterial and viral infections. The nasopharyngeal swab for H1N1 was negative as well as the results of galactomannan in serum and BAL. In view of the ineffectiveness of empiric antibiotic treatment and high suspicion of hypersensitivity pneumonitis (HP), on the same day (ay 8 after admission) we started high dose pulsed boluses of corticosteroids (methylprednisolone 1 gr IV per day) and immunoglobulin treatment (400 mg/Kg IV). Soon after the initiation of steroid therapy there was a rapid and significant improvement in his clinical condition.

High dose steroid therapy and i.v. immunoglobulins were continued for five days, and then the steroid treatment was gradu-

ally tapered. A new chest CT scan (figure 1c) performed seven days after starting steroid and immunoglobulin therapy (day 15 after admission) revealed a significant clearance of previous pulmonary findings. Search for anti-nuclear, anti-neutrophil cytoplasmic and antiglomerular basement membrane antibodies (i.e. ANA, ANCA, GBM) turned negative, providing a very low probability of an associated connective tissue disease. Cytological examination of BAL fluid was negative for neoplastic cells. All the available clinical and instrumental data, along with the rapid clinical and radiological response with high dose steroids and i.v. immunoglobulins, suggested a clinical ("*ex-adiuvantibus*") confirmation of an immune-mediated origin of the syndrome. We supposed that a diagnosis of hypersensitivity interstitial pneumonitis with diffuse alveolar hemorrhage was the most fitting for this syndrome.

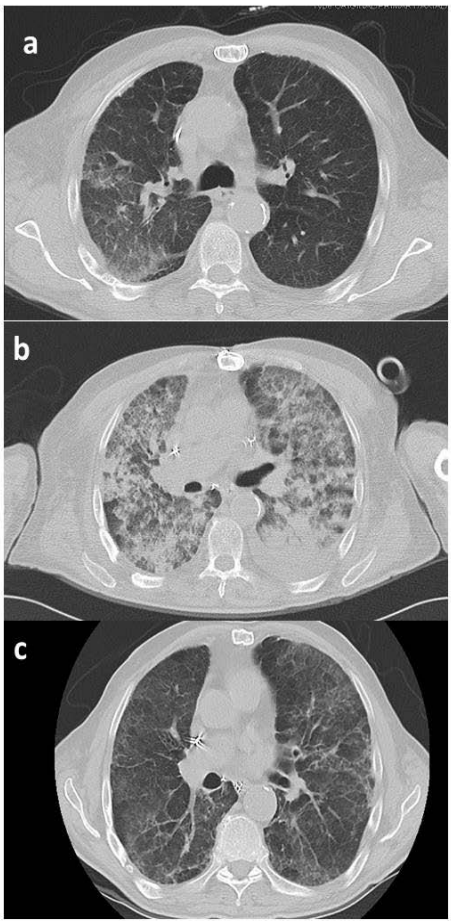

Figure 1. Contrast-enhanced computed tomography scan at admission (a), 8 days after admission ,showing thickening of interlobular septa, massive diffuse alveolitis with extensive patchy and confluent ground glass opacities in both lung fields (b) and 15 days after admission (seven days after starting steroid and immunoglobulin therapy) showing significant clearance of previous pulmonary findings (c).

Discussion

The intravesical administration of BCG-RIVM has been proven effective against superficial non muscle invasive bladder cancer [8]. Complications of BCG infection - either local or systemic - have been reported with an incidence of 10-15% [15]. Serious adverse effects are infrequent and present in less than 5% of cases [9]. Compared to commonly induced granulomatous inflammatory changes in the bladder, pneumonitis is a rare complication of this immunotherapy that is seen in less than 0.7% patients following the repeated administration of BCG [8,14]. A hypersensitivity reaction rather than a disseminated BCG infection is suspected in the pathogenesis of this disorder in view of the fact that mycobacteria are not detected in these patients. In literature there are few reports on HP following intravesical instillation of BCG [3,8] and to our knowledge no cases have been reported with hemorrhagic alveolitis due to diffuse alveolar damage. HP is a rare immunologically mediated lung disease caused by repeated exposition to organic antigens and DAH is the most severe and life threatening form of HP. DAH is a clinical syndrome, caused by several conditions (Table 1), characterized by widespread bleeding into the acinar portion of the lung due to microvascular injury [11]. It is defined by the clinical trial of hemoptysis, anemia and progressive hypoxemia. The diagnosis of DAH relies on clinical suspicion combined with laboratory, radiologic, and pathologic findings whenever available. DAH should be distinguished from other causes of pulmonary hemorrhage caused by localized pulmonary abnormalities of the bronchial circulation [10]. Early bronchoscopy with BAL is generally required to confirm the diagnosis of DAH and to rule out difficult infections. Early recognition is crucial, because prompt diagnosis and treatment are the most important factors increasing the probability of survival [7]. Factors associated with mortality include the needing of invasive mechanical ventilation, and the presence of renal failure and infections. Bacterial infections have been reported frequently in patients with DAH, as well as invasive fungal infections especially pulmonary aspergillosis [11]. The mortality rate remains high despite the use of aggressive multiple medical and supportive therapies. From a pathophysiological point of view HP with DAH is most likely due to immune complex mediated necrotizing alveolitis and bronchiolitis. This can be explained by a hypersensitivity phenomenon following instillation of BCG, especially in presence of traumatic bladder catheterization (confirmed by gross hematuria as occurred in this case), that allows organic BCG antigens to reach rapidly the circulatory system [12-14]. HP, and its most severe manifestation with DAH, should be always considered in patients with acute respiratory failure, and a compatible clinical and radiological picture, soon after immunotherapy with BCG especially when a traumatic procedure has been reported. A prompt diagnosis will permit to start as soon as possible an adequate and life-saving treatment with high dose steroids, i.v. immunoglobulins and eventually plasma exchange [3,16]. To the best of our knowledge this is the first report of HP with DAH due to BCG immunotherapy. This case was reported to the Italian authority on pharmacovigilance (AIFA – Agenzia Italiana del Farmaco).

Infectious diseases	Staphylococcus aureus Leptospirosis Hantavirus Anaerobic bacteria Invasive aspergillosis
Connective tissue diseases	Systemic lupus erythematosus (SLE) Ankylosing spondylitis (AS) Rheumatoid arthritis Mixed connective tissue disease
Lung diseases	Pulmonary embolism Hypersensitivity pneumonitis Pulmonary capillaritis Pulmonary veno-occlusive disease ARDS Sarcoidosis Idiopathic pulmonary hemosiderosis
Cancer	Uterine leiomyosarcoma Small cell lung cancer Hematologic malignancies
Vasculitis	Granulomatosis with polyangiitis (formerly Wegener's Granulomatosis) Churg Strauss disease Microscopic Polyangiitis Goodpasture's syndrome Henoch Schonlein purpura Cryoglobulinemic vasculitis
Cardiac disorders	Left ventricle systolic and/or diastolic dysfunction Valvular heart disease (e.g. mitral stenosis)
Coagulation disorders	Idiopathic thrombocytopenic purpura Antiphospholipid antibody syndrome Disseminated intravascular coagulopathy Anticoagulant and/or antiplatelet treatment
Organ transplantations	Autologous bone marrow transplantation Acute lung transplantation rejection
Toxic agents	Cocaine Crack Cannabis

	Isocyanates Retinoic acid
Drugs	Amiodarone Methotrexate Amphetamine Penicillamine Propylthiouracil Ketorolac Nitrofurantoin Clomiphene
Barotrauma related diffuse alveolar hemorrhage	

Table 1. Causes of diffuse alveolar hemorrhage.

References

1. Bourke SJ, Dalphin JC, Boyd G, McSharry C, Baldwinz CI et al. Hypersensitivity pneumonitis: current concepts. Eur Respir J Suppl. 2001, 32: 81s–92s.

2. Mohr LC. Hypersensitivity pneumonitis. Curr Opin Pulm Med. 2004, 10(5):401-411.

3. Um SJ, Lee SK, Yang DK. Hypersensitivity Pneumonitis Following Intravesical Bacille Calmette-Guérin Immunotherapy for Superficial Bladder Cancer. J Investig Allergol Clin Immunol. 2009, 19(3): 230-232.

4. Molina JM, Rabian C, D'Agay MF, Modai J. Hypersensitivity systemic reaction following intravesical bacillus Calmette-Guerin: Successful treatment with steroids. J Urol. 1992, 147(3):695-697.

5. Lyons D, Miller I, Jeffers A. Systemic hypersensitivity reaction to intravesical BCG. Scott Med J. 1994, 39(2):49-50.

6. Reinert KU, Sybrecht GW. T helper cell alveolitis after bacillus Calmette-Guerin immunotherapy for superficial bladder tumor. J Urol. 1994, 151(6):1634-1637.

7. Suk Park M. Diffuse Alveolar Hemorrhage. Tuberc Respir Dis (Seoul). 2013; 74(4): 151–162.

8. Lamm DL, Van der Meijden PM, Morales A, Brosman SA, Catalona WJ et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol. 1992, 147(3):596-600.

9. To U, Kim J, Chia D. Disseminated BCG: Complications of Intravesical Bladder Cancer Treatment. Case Reports in Medicine, 2014.

10. Lara AR, Schwarz MI. Diffuse Alveolar Hemorrhage. Chest. 2010, 137(5):1164-1171.

11. Martínez-Martínez MU, Abud-Mendoza C. Diffuse Alveolar Hemorrhage in Patients With Systemic Lupus Erythematosus. Clinical Manifestations, Treatment, and Prognosis. Reumatol Clin. 2014,10(4): 248-253.

12. Rawls WH, Lamm DL, Lowe BA, Crawford ED, Sarosdy MF et al. Fatal sepsis following intravesical bacillus Calmette-Guerin administration for bladder cancer. J Urol. 1990,144(6):1328-1330.

13. Van der Meijden AP. Practical approaches to the prevention and treatment of adverse reactions to BCG. Eur Urol. 1995, 27 (Suppl 1):23-28.

14. Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ et al. Incidence and treatment of complications of bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol. 1992, 147(3):596-600.

15. Rischmann P, Desgrandchamps F, Malavaud B, Chopin DK. BCG intravesical instillations: recommendations for side-effects management. Eur Urol. 2000, 37 (Suppl 1):33-36.

16. Green RJ, Ruoss SJ, Kraft SA, Duncan SR, Berry GJ, Raffin TA. Pulmonary capillaritis and alveolar hemorrhage. Update on diagnosis and management. Chest. 1996 , 110(5):1305-1316.