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CASE REPORT WITH REVIEW OF LITERATURE

MACROPHAGE ACTIVATION SYNDROME (MAS) SECONDARY TO MYCOBACTERIUM BOVIS CYSTITIS FOLLOWING INTRAVESICAL INSTILLATION OF BACILLUS CALMETTE–GUÉRIN (BCG) VACCINE: A CASE REPORT WITH REVIEW OF LITERATURE

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Abstract

Background: Intravesical Bacillus Calmette–Guérin **(**BCG) vaccine instillation is widely used for the treatment of superficial bladder cancer. While mild non-infectious problems have mostly been reported with intravesical BCG instillation, significant local and systemic complications, albeit low, have also been documented. Macrophage activation syndrome (MAS) is a potentially serious condition characterized by a hyperinflammatory state occurring secondary to infections, malignancies, and autoimmune diseases. Intravesical BCG is internalized into tumor cells, initiating local and systemic immune responses, leading to MAS.

Case Summary: We report the case of a 61-year-old male patient with high-grade papillary bladder carcinoma who was diagnosed with macrophage activation syndrome (MAS) in association with Mycobacterium bovis (M bovis) cystitis following the fifth dose of intravesical BCG instillation. He was put on high-dose oral steroids prednisolone 1mg/kg/day for MAS along with antitubercular targeting M bovis infection. There was a dramatic clinical responsefrom Day 7 of treatment with a drastic reduction in serum ferritin levels from day 12. There are only 6 cases of MAS in association with intravesical BCG instillation reported in the literature to date. All were male patients with the median age being 67 years which was similar to our patient's age. Intravenous Immunoglobulin (IVIG) (5/6, 83.33%), high-dose steroids (6/6, 100%), and antitubercular drugs (2/6, 33.33%), Vinblastine (1/6, 16.66%) were used in these cases for the treatment of the same.

Conclusion: The diagnosis of MAS in a setting of intravesical BCG immunotherapy requires a high index of suspicion as MAS has been rarely found to be associated with BCG therapy and there is an increased risk of mortality when this condition remains untreated.

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Introduction:-

Macrophage Activation Syndrome (MAS) is a systemic hyperinflammatory syndrome characterized by fever, elevated serum ferritin and other markers of systemic inflammation, inappropriately low blood cell counts, disseminated intravascular coagulopathy, hepatitis, central nervous system (CNS) inflammation and high risk for progression to multiple organ dysfunction. The presentation of MAS can be highly variable in the early stages The patients may not satisfy the diagnostic criteria of Hemophagocytic lymphohistiocytosis syndrome (HLH) at the initial stages. Hence, a delay in initiating treatment may result in rapid deterioration and death [1].

Bacillus Calmette-Guérin (BCG), is a live attenuated strain of Mycobacterium bovis (M. bovis) that is administered intravesically as an adjuvant immunotherapy for the treatment of non-muscle invasive bladder cancer (NMIBC). The BCG is thought to activate the local immune response leading to the death of tumor cells, with high efficacy and good tolerance [2]. Complications induced by BCG can occur; usually, these are local self-limiting consisting of fever, malaise, and bladder irritation due to cystitis [3]. However, systemic complications like fever without sepsis, granulomatous hepatitis, pneumonitis, reactive arthritis, spondylodiscitis, Guillain–Barre syndrome have been reported with intravesical BCG instillation. MAS is one of the rare complications of intravesical BCG therapy with very few cases reported in the literature so far. The pathophysiology of these systemic complications is poorly understood. The plausible mechanism has been hypothesized as BCG being internalized in the tumor cells, leading to the activation of antigen-presenting cells (APCS), further producing cytokines and chemokines. These cytokines and chemokines thereafter cause the activation of neutrophils, monocytes, macrophages, B cells, T cells, and natural killer cells resulting in systemic hyperinflammation [4]. We report the case of a patient with superficial bladder cancer who developed BCG cystitis and secondary Hemophagocytic Lymphohistiocytosis (HLH) following intravesical BCG instillation.

Case Presentation:-

Chief Complaints

A 61-year-old male patient, presented with high-grade intermittent fever for the past 1 month.

History of present illness

The patient started developing fever for 1 month, which was intermittent with the maximum axillary temperature recorded around 39.5°C. The febrile episodes were associated with anorexia and fatigue, without any specific localising symptoms.

History of Past Illness

He was diagnosed with high-grade papillary urothelial carcinoma with invasion into lamina propria (Stage G3PT1) 4 months prior to admission for which he underwent transurethral resection of bladder tumor (TURB). He was planned for weekly dosage of intravesical BCG instillation for 6 weeks following TURB. However, a day after the fifth dose of intravesical BCG, he started having intermittent high-grade fever and fatigue. He was treated with a 7-day course of cefuroxime.Despite persistent fever, he was given the sixth (final) dose of BCG. He received another 2-week course of Intravenous (IV) antibiotics meropenem and levofloxacin without any resolution of febrile episodes. He was thereafter referred to our hospital for evaluation of fever and further management.

Personal and Family History

He was a known smoker with a history of 10 pack-years of smoking. There was no history of contact with tuberculosis. There was no significant family history.

Physical Examination

On admission, he was alert, and oriented but febrile with an axillary temperature of 39.5°C, pulse rate of 115 beats/min, and blood pressure of 130/80 mm Hg. His respiratory rate was 20 per min and oxygen saturation was 98% on pulse-oximetry. He had mild pallor and icterus without edema. He had a soft, tender hepatomegaly with a liver span of 14 cm. The remaining systemic examination was non-contributory.

Laboratory Tests

Laboratory tests revealed normocytic normochromic anemia with haemoglobin (Hb) of 9.0g/dL, leukopenia with relative lymphocytosis (Total leucocyte count (TLC) 3100/mm^3 Neutrophil 38%, Lymphocytes 55%) with normal platelet count. Liver Function Tests were deranged with total bilirubin of 5.97mg/dL, direct bilirubin of 3.37mg/dL, aspartate aminotransferase (AST) 195U/L, alanine aminotransferase (ALT) 157U/L, and alkaline phosphatase (ALP)

822U/L. The serum inflammatory markers were markedly elevated with C-reactive protein (CRP) of 209 mg/L (< 6 mg/L) and ferritin levels of 5556 ng/ml (20–150 µg/l). However, her erythrocyte sedimentation rate (ESR) was normal at 10 mm in the first hour. Serum triglyceride levels were high at 523mg/dL (< 150 mg/dl). Serum fibrinogen levels were low at 260 mg/dl in a backdrop of normal ESR levels. Renal function tests and coagulation profiles were within normal limits. His screening test for Human Immunodeficiency virus (HIV), Cytomegalovirus (CMV), Parvovirus B19, Ebstein-Barr virus (EBV), scrub typhus, leptospirosis, brucellosis, and visceral leishmaniasis were negative. Peripheral blood smear did not reveal any malignant cells or parasites. Blood and urine cultures showed no growth. He was also screened for infective endocarditis with 2D echocardiography which did not show any vegetation. Real-time Polymerase chain reaction (PCR) test by Truenat for Mycobacterium tuberculosis Complex turned out to be positive in the urine sample. This test was done 1 month after the last dose of BCG instillation in bladder. Mycobacterium bovis is a part of the Mycobacterium tuberculosis complex infection and can give rise to positive real-time PCR test for Mycobacterium tuberculosis Complex [5]. However, he did not have any other systemic manifestation of disseminated mycobacterial bovis infection

He was thus, diagnosed as a case of Macrophage activation syndrome based on HScore of 214 for Reactive Hemophagocytic Syndrome with an optimal cut-off score of 169 [6] in a background of Mycobacterium bovis cystitis induced by intravesical BCG instillation. However, Bone marrow aspiration was normocellular and negative for any hemophagocytes, abnormal cells, LD bodies or AFB stain.

Imaging Examinations
The Ultrasound abdomen revealed an enlarged liver (165mm) and spleen (132mm). Computed tomography (CT) of abdomen also revealed hepatomegaly and splenomegaly without any focal lesions

Final Diagnosis
Macrophage Activation Syndrome secondary to Mycobacterium bovis cystitis following intravesical instillation of BCG.

Treatment
The patient was started on a triple Anti-tubercular regimen consisting of Isoniazid 300 mg OD, Rifampicin 450 mg OD, and Ethambutol 800 mg OD as Pyrazinamide does not have any effect on Mycobacterial bovis species. Along with antitubercular medication, he was given high-dose oral prednisolone (1mg/kg/day) for treatment of MAS.

Outcome and Follow-Up
The patient showed remarkable clinical improvement and became afebrile seven days after initiation of treatment. A remarkable improvement in serum ferritin was noted on Day 12 after starting high-dose oral steroids. The patient was discharged with Antitubercular medication (Isoniazid, Rifampicin, and Ethambutol) for 6 months with oral prednisolone @1 mg/kg body weight for 1 month followed by gradual tapering of steroid dose over the next 3 months. Throughout, the follow-up period, the treatment regimen was well tolerated and the patient remained afebrile with improvement in general condition. The laboratory findings are summarized in Table 2.

Discussion:-

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening state of immune hyperactivation that arises in the setting of genetic mutations with infectious, inflammatory, or neoplastic triggers [7]. Hemophagocytosis may be detected on bone marrow aspiration or biopsy from the lymphoid organs, although in the early stages, the bone marrow may be negative [8]. Intravesical instillation of BCG can cause several local and systemic complications summarized in Table 2 [9]. Macrophage activation syndrome or secondary HLH due to intravesical BCG administration is rare with only a few cases reported in the literature [10,11]. The mechanism of intravesical BCG-induced MAS is incompletely understood. Once in the bladder, it is hypothesized that BCG comes in contact with urothelial cells first. If the tissue is damaged, BCG is exposed to bladder-resident macrophages [12]. BCG is internalized by the tumor cells in the high-grade lesions and not by the normal urothelial cells [13]. Once internalized, BCG activates both local and systemic immune responses. Resident urothelial cells and antigen-presenting cells (APCs), on activation by intravesical BCG, lead to the production of cytokines and chemokines. These cytokines and chemokines attract granulocytes and mononuclear cells to the bladder [14], resulting in granuloma formation. Cytokines and chemokines also lead to the recruitment of neutrophils, monocytes, macrophages, T cells, B cells, and natural killer (NK) cells [15, 16]. Neutrophils exert an antitumor effect by phagocytic activity and release of lytic antimicrobial enzymes as well as proapoptotic factors. Neutrophils may also

mediate monocyte and CD4+ T cell infiltration into the bladder [17]. The other cells like the CD8+ T cells, NK cells and macrophages are also involved in the BCG-induced systemic hyperinflammatory state [18]. Treatment of MAS consists of high-dose oral or IV glucocorticoids or intravenous immunoglobulin (IVIG) at a dose of 0.4-1g/kg/day for 2-5 days [19]. Although IVIG would have been a better option for infection-associated MAS, we chose 1mg/kg oral prednisolone to treat this condition, owing to the non-availability of the former in a resource-constrained setting. Moreover, with a concurrent antitubercular regime, we expected less chances of dissemination of Mycobacterium bovis despite prolonged immunosuppression. Triple Anti-tubercular therapy with rifampicin, isoniazid, and ethambutol for 6 months is considered for M. bovis as it is resistant to pyrazinamide [20]. Of notice, even though mortality associated with HLH secondary to tuberculosis is very high 45-50% [21], all reported patients with BCG-associated HLH have recovered except one [24].

There are only 6 cases of BCG-induced MAS reported in the literature to date. The clinical profile and treatment regimens used in these cases are listed in Table 3. The median age group in these patients was 67 years (range 49-78 years). Our patient was 61 years old belonging to the same age group reported previously. All were males as in our case. Of the six cases of intravesical BCG-associated MAS reported in literature, three of them developed MAS, early during BCG immunotherapy, while the other three developed the same after 6 doses of BCG immunotherapy. Our patient developed MAS after the fifth dose of intravesical BCG. IVIG, the mainstay of treatment in infection-associated MAS, was used in five out of the six reported cases. One of the reported cases was treated only with high-dose dexamethasone. Vinblastine was also used as a part of the regime to manage MAS in another reported case. Our patient was managed with high-dose oral prednisolone and anti-tubercular therapy.

Conclusion:-

MAS is a hyperinflammatory syndrome that can very rarely occur as a secondary effect following BCG immunotherapy. The diagnosis of this condition requires a high index of suspicion. Initiation of appropriate immunosuppressive therapy targeting MAS and anti-tubercular regimen targeting M bovis can resolve the inflammation without increasing the chances of dissemination.

Table 1:- Incidence of complications induced by intravesical BCG immunotherapy for Non-Muscle Invasive Bladder Cancer [9].

Genitourinary Complications	Incidence (%)	Systemic Complications	Incidence (%)
Cystitis	27-95	Fever (>38.5°C)	2.9
Bladder contracture	<1	Mycotic Aneurysms	0.7-4.6
Bladder ulceration	1.5	Miliary pulmonary tuberculosis	0.4
Penile lesions*	5.9	Granulomatous hepatitis	0.7-5.7
Tuberculous epididymo-orchitis	0.4	Reactive arthritis	0.5-5.7
Symptomatic prostatitis	10	Tuberculous Spondylitis	3.5
Ureteral obstruction	0.3	BCG sepsis	0.4
Kidney infections	0.3-0.5	Rare complications#	

BCG- Bacillus Calmette–Guérin
*Penilelesionsconsisted of nodules, papules, plaques, or ulcerswith or without inguinal lymphnodeenlargement.
Rare complications include Central Nervous System infection, ocular inflammation, HLH

Table 2:- Laboratory findings during admission, at hospitalisation, and follow-up.

Blood Parameters	Admission	Day 12 Treatment initiation	Day 20 after Discharge	2months after discharge
WBC (per mm$^{3)}$	3100	3120	4100	5800
Pol/Lymph (%)	38/55	32/56	38/58	65/30
Hb (g/dl)	9.3	9.2	9.1	9.7
PLT (per mm$^{3)}$	233000	201000	266000	288000
ESR (mm in the first hour)	10	12	18	35
Total Bilirubin (mg/dl)	5.97	4.81	4.76	1.2

Direct Bilirubin (mg/dl)	3.37	3.29	2.1	0.5
AST (U/L)	195	189	153	36
ALT (U/L)	157	161	124	27
ALP (U/L)	822	784	697	387
Sodium (meq/L)	125	129	131	144
Potassium (meq/L)	3.71	4.5	3.79	3.08
Triglyceride (mg/dl)	523	388	304	199
Ferritin (ng/ml)	5556	2200	1300	762

ALP- Alkaline Phosphatase; ALT- Alanine Aminotransferase; AST- Aspartate Aminotransferase; ESR- Erythrocyte Sedimentation Rate; Hb- haemoglobin; Lymph- Lymphocytes; PLT- Platelet; Pol- Polymorphs; WBC- White blood cell;

Table 3:- Clinical profile and treatment regimens of secondary Hemophagocytic Lymphohistiocytosis cases following Intravescicular BCG instillation.

Author	**Age (in years)/ Gender)**	**Onset of Symptoms**	**Treatment Received**
Schleinitz N (2002) [22]	49 years/M	One month after 6th cycle of BCG instillation	IVIG, Prednisolone, Vinblastine
Thierry Thevenot (2006) [23]	78 years/M	Few hours after 1st cycle of BCG instillation	Methylprednisolone, IVIG, ATT
Saumya Misra (2013) [10]	70 years/M	Following 2nd cycle of BCG instillation	IVIG, Methylprednisolone, ATT
Manganas K (2022) [11]	64 years/M	Few hours after 6th cycle of BCG instillation	High dose dexamethasone 10mg/m^2
Stevan Stojanović (2023) [24]	55 years/M	Just after 2nd cycle of BCG instillation	IVIG, Methylprednisolone
G. D. Liatsos (2023) [25]	73 years/M	Few hours after the second instillation of the second maintenance course (eighth instillation in total)	Methylprednisolone, IVIG
Current study (2024) (Misra et al)	61 years/M	Following fifth dose of intravesical BCG	Prednisolone (1mg/kg), ATT

ATT- Anti-tubercular therapy; BCG- Bacillus Calmette–Guérin; IVIG- Intravenous immunoglobulin

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