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Tubercular disease caused by bacillus of Calmette-Guerin administered as a local adjuvant treatment of relapsing bladder carcinoma. Pathogenetic, diagnostic and therapeutic issues, and literature review

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Abstract

Two exemplary case reports of respiratory granulomatous infection caused by bacillus of Calmette-Guerin (BCG) in patients who were repeatedly treated with local, intravesical adjuvant BCG therapy for a relapsing transitional bladder carcinoma, are outlined and discussed, on the ground of the cumbersome diagnostic and differential diagnostic process (especially when a prior tuberculosis and a concurrent chronic obstructive pulmonary disease are of concern), and an updated literature revision. Only four cases of respiratory BCG-itis (pulmonary tuberculosis-like forms), have been reported until now to the best of our knowledge (two of them following bladder instillation of BCG). One episode of ours represents the first described case with a dual, concomitant granulomatous localization of BCG-itis, also involving the genitourinary tract.

Key words: Bacillus of Calmette-Guerin, bladder carcinoma, local therapy, infection dissemination, BCG-itis, pulmonary and genito-urinary localizations, differential diagnosis

Introduction

Bladder carcinoma is represented in around 90% of cases by urothelial forms (characterized by transitional cells), which usually have a multifocal occurrence and course. At the time of diagnosis, over two thirds of these malignancies have a superficial (mucosal or laminar) localization. The conventional management of localized bladder carcinoma relies on the trans-urethral resection, followed by an endovesical therapy (either cytotoxic or immune therapy, especially recommended in more advanced forms).

The bacillus of Calmette-Guerin (BCG) is an attenuated strain of Mycobacterium bovis (a potentially pathogenic Mycobacterium in humans), initially produced as a vaccine against tuberculosis, and largely employed with this indication since over seven decades, until now1-6. Given to its local immunomodulatory properties, BCG preparations are administered as a part of an adjuvant treatment of bladder adenocarcinoma since the year 19727, through repeated local intravesical instillations. During the last 36 years, a number of clinical trials confirmed the efficacy of local BCG treatment in reducing both progression and recurrences of bladder carcinoma8-12. In particular, the rationale of local adjuvant treatment carried out with cycles of intravesical instillations of BCG solutions aims to strengthen the specific anti-neoplastic immune response, in the attempt to eradicate residual disease foci and reduce the risk of subsequent cancer relapses11,12. The BCG preparations administered in form of intravesical instillations are indicated until now for the adjuvant management of bladder carcinoma with superficial localization, i.e. in situ carcinoma, papillary carcinoma limited to mucosa (stage
Ta), papillary carcinoma extended to lamina propria, but not involving muscular layers (stage T1), or every combination of the above-mentioned conditions. During the subsequent urological follow-up, despite specific treatment, around 50-70% of these neoplasms have a relapse, often burdened by a progression of tumoral grading.11,12

As to the immunopathologic rationale of BCG administration against bladder carcinoma, the local immune response elicited by BCG starts with phagocyte cell activation. After recognizing some BCG antigens the phagocytes trigger the secretion of a cascade of numerous cytokines, including interleukin-12, interferons, and the tumoral necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). The next step in the elicited immune response is represented by the induced polarization of T-helper-0 (Th-0) lymphocytes towards T-helper-1 (Th-1) lymphoid cells. The expansion and activation of Th-1 lymphocyte subset is able to potentiate the anti-neoplastic response carried out by T-cytotoxic lymphocytes (CTL) and that of the so-called natural killer (NK) cells, through the release of a series of other cytokines, with a relevant role played by interleukin-2.10,12,14,15

Aim of our work is to present two exemplary case reports of patients treated with local BCG immunotherapy for a relapsing urothelial bladder carcinoma, who developed a severe M. bovis respiratory infection, whose diagnostic pathway was particulary complicated due to co-existing chronic pulmonary diseases (prior pulmonary tuberculosis, and chronic obstructive pulmonary disease or COPD), and a second, BCG-related isolated genito-urinary lesion retrieved in one case of ours.

Case reports

First case report

A 77-year-old patient with a superficial, relapsing bladder adenocarcinoma (stage T1, grade 2), known since three years, suffered from three local relapses of the urothelial cancer, always managed with local endoscopic surgery, and later submitted to an adjuvant BCG treatment, lasting since 18 months. After his last month of his weekly cycles of local, endovesical immunotherapy with BCG instillations (75 mcg of BCG diluted with 50 mL of saline), he was hospitalized in the year 2008 because of the appearance and the rapid worsening of hyperpyrexia, malaise, weight loss, and toxemia, which were not responsive to two attempts of empiric broad-spectrum antimicrobial chemotherapy, carried out with levofloxacin (10 days), followed by ceftriaxone (three days).

After an initial standard chest X-ray study which showed a comprehensive picture of COPD, and multiple upper lobes fibrotic lesions compatible with a prior pulmonary tuberculosis, a high-resolution CT scan (HRCT) and a contrast-enhanced thorax CT scan demonstrated a diffuse involvement of all lung parenchima by an extremely elevated number of small, punctiform nodular lesions, extremely suggestive of miliary mycobacterial/tubercular disease (Figure 1). Multiple radiological signs of a prior lung tuberculosis were present at upper lobes: they included extensive fibrosis, diffuse centrolobular emphysematous lesions, and diffuse pleural thickening with sparse calcifications, while mediastinal lymph nodes were within normal limits, although some calcified nodes were shown.

Figure 1. A contrast-enhanced CT scan of the thorax of our first patient. Multiple, micronodular miliary BCG localizations are shown, reproducing the picture of a miliary tuberculosis. A concurrent chronic obstructive pulmonary disease (COPD), and fibrotic remnants of a prior, juvenile lung tuberculosis are also present.

A contrast-enhanced CT scan of the abdomen and pelvis did not show lesions compatible with futher miliariform BCG lesions involving abdominal organs: an uniform, mild thickening of bladder walls was evident, as expected by the known underlying, relapsing urothelial carcinoma.

Blood and urine cultures, and also microbiological examination of a transbronchial biopsy specimen and bronchoalveolar lavage (BAL) fluid, did not allow the recognition and
culture of any microorganisms, including mycobacteria. On the other hand, an elevated number of lymphoid cells, histiocytes, reactive bronchial cells, and cylindroform cells of bronchial epithelium was demonstrated at BAL study, while a granulomatous-tubercular like picture with lymphoid-histiocyte-giant cell infiltrate was demonstrated at histopathology.

On the other hand, a mild positivity of Mantoux intradermal reaction, was confirmed by a frankly positive interferon-gamma release assay (IGRA, QuantiFERON-TB Gold, Cellestis, Vic., Australia) 16.

General laboratory examinations showed only an elevated serum C-reactive protein (6.76 mg/dL), but a normal ESR, and no significant abnormalities of total leukocyte count and differential.

On the ground of a diagnosis of miliary pulmonary BCG-itis, a treatment was immediately started with associated rifampicin, isoniazid, ethambutol, and levofloxacin. The treatment was well tolerated from a clinical and laboratory point of view, and after three weeks our patient achieved a progressive defervescence, an amelioration of respiratory signs and symptoms, and a slowly progressive resolution of pathological signs at subsequent imaging examinations, allowing hospital discharge and an outpatient follow-up. Anti-tubercular therapy lasted for a comprehensive period of 9 months (during the last three months it was conducted with rifampicin-isoniazid only), and was well tolerated. A novel HRCT, repeated after six weeks, showed an almost complete disappearance of parenchymal miliary lesions, while the remaining abnormalities, mostly referred to COPD and prior tuberculosis, remained unchanged. Bladder carcinoma remained under control until the last urological visit end endoscopy, carried out two months after hospital discharge.

**Second case report**

A 58-year-old man with a superficial, multifocal, transitional carcinoma of the bladder already relapsed since 4–5 years, started a local immunotherapy with endovesical BCG instillations around one year before the occurrence of the BCG-related complications. After a first cycle of six weeks of BCG administrations followed by a three-month interval, the treatment was resumed with one BCG instillation per month, and always proved sufficiently well tolerated, save some intercurrent episode of mild and self-limiting hematuria. Three months later, after demonstrating a local tumoral recurrence, which required a cycle of intravesical mitomycin therapy at standard dosages, a further series of BCG immunotherapy cycles was proposed (81 mcg of BCG diluted with 50 mL of saline solution). During this last adjuvant BCG therapy, our patient showed a fastidious, minimally productive cough, associated with overwhelming fever, not responsive to large-spectrum empiric antibiotic therapy with ciprofloxacin and beta-lactams. Owing to the persistance of these signs and symptoms, our patient was hospitalized at the end of year 2002.

The clinical history pointed out a probable pulmonary tuberculosis three decades before, whose diagnosis was mainly based on imaging and clinical remnants. Three years before admission, a spontaneous pneumothorax (as a complication of a chronic, bullous pulmonary emphisema), required a surgical intervention, which included a pleural decortication. Upon admission, a first chest X-ray film showed multiple specific sequelae, including bilateral, apical pleural thickening, together with a diffuse chronic obstructive pulmonary disease (COPD), with co-existing chronic bronchitis and an evident emphisematous evolution. A HRCT of the thorax gave a better picture of the diffuse, emphisematosus COPD, prevailing at upper lobes, where areas of paramediastinic paracicatritial, and centrolobular emphisema determined a number of bullous lesions, with underlying extensive fibrosa hyperdense bands. Multiple calcified lymph nodes were detected in various thoracic sites, as signs of the prior, juvenile tuberculosis disease.

Notwithstanding a negative Mantoux intradermoe reaction, the clinical picture of cough, fever, and later dyspnea posed a suspicion of pulmonary BCG-itis, in a patient with prior lung tuberculosis, a concomitant COPD, and a moderately elevated ESR (30, first hour). As a consequence, an initial associated therapy including rifampicin, isoniazid, ethambutol, streptomycin and ciprofloxacin was started, together with supportive treatments. A bronchoscopy with transbronchial biopsies and BAL, allowed to recognize a histopathological picture of multiple-foci chronic granulomatous pneumonia with evidence of nodular-epithelioid and necrotizing evolution, a macrophage and giant-cell tubercular-like infiltrate, with associated diffuse endoalveolar fibrosis. Further investigations performed on BAL fluid showed a prevalence of macrophage and lymphoid cells, together with cylindrical bronchial cells, but both microscopic and culture search tested negative, for mycobacteria too.

One week later, a second HRCT pointed out the appearance of a dishomogeneous parenchymal infiltrate at the right side associated with a modest homolateral pleural reaction. Both blood and urine cultures performed upon hospitalization tested negative, while a specific mycobacterial serodiagnosis performed with the TB-test A60 available at that time’s proved frankly positive, demonstrating elevated specific IgG-IgM antibody titers. Due to persisting of irregular hyperpyrexia, and the worsening of cough and dyspnea, complicated by hypoxemia (PaO2 70 mmHg), a low-dose steroid therapy was added. Three weeks after the first HRCT, a further thorax imaging showed a worsening, due to a diffuse centro-alarieal emphisema at upper lobes, associated with multiple consolidative parenchymal areas involving medium and lower lobes, with predominant sub-pleural localization. Diffuse central-lobular micronodules were present together with a diffuse gross interstitial involvement, compatible with a subacute pneumopathy, complicated with a fibrotic evolution. Despite ongoing antimicrobial and steroidal treatment, two weeks later another HRCT showed an extension of consolidative infiltrates at postero-lateral segments of lower pulmonary lobes.

After a slow, but progressive amelioration of clinical-respiratory picture, after 5 weeks of hospitalization our patient was discharged with the indication to continued anti-tubercular therapy for one comprehensive year. The subsequent follow-up included a satisfactory tolerability of anti-tubercular therapy (reduced to isoniazid and ethambutol only...
during the last three months). One year after discharge, a novel HRCT showed an advanced, diffuse centrolobular and subpleural emphysematous lesions, in absence of parenchymal infiltrates and nodular lesions, and relevant, novel mediastinal adenopathies. However, a functional respiratory assessment pointed out a limitation of respiratory flow at low-medium pulmonary volumes, and a compromised alveolar-capillary diffusion, when compared with the same evaluation performed one year before. A perfusional scintigraphy documented a diffuse dishomogeneity of distribution of labelled macroalbumin aggregates, with a pulmonary differential diffusion limited to 50%.

From the urologic point of view, a double biopsy of an indolent, penile nodule performed three months before discharge, confirmed another localization of a tuberculosis-like granulomatous lesion at histopathologic studies. Therefore, BCG-itis was responsible for two, concurrent different disease localizations (pulmonary, and genital ones), both following a potential hematogenous dissemination of attenuated BCG bacilli.

Six years after discharge (in December 2008), our patient has a stable remission of his bladder carcinoma, and no sign of activity of prior BCG-caused distant-site localization was appreciated. The penile lesion was cured, while the HRCT control confirmed a severe COPD, complicated by multiple fibrous-calcific reliquates, and the functional respiratory tests remained significantly compromised.

Discussion

The anti-tubercular vaccine BCG, largely employed in the immunization of children and adults in areas which are endemic for tuberculosis, and in the prevention of disseminated, miliary, and central nervous system disease in health care personnel and other subjects with a potential professional or familial exposure to tuberculosis1-4, suffers from a non-negligible rate of untoward events, more frequently represented by local inflammatory lesions interesting the injection and regional sites, usually associated with fever and satellite adenopathy (sometimes evolving into a suppurrative form), while focal, long-distance localizations are significantly more frequent, followed by extremely rare episodes of systemic dissemination of the attenuated M. bovis bacillus (the so-called BCGitis), usually developing in patients with an underlying primary-secondary immunodeficiency5,18, but sometimes observed also in apparently immunocompetent subjects5-6.

A recent surveillance project conducted in Ireland on a broad pediatric population which underwent BCG vaccination7, after a median latency of 13 weeks showed the onset of either limphadenitis (suppurative or non-suppurative forms), or abscesses at the inoculum site, or both complications, with a crude frequency of one case every 931 children who received BCG (while one subject of 1,543 developed a suppurative adenitis, which required surgical intervention in around one half of cases)5.

Again in developmental ages, a Canadian study8 allowed to observe also cases of bone localization and systemic dissemination of vaccinal BCG, which in some cases led to a fatal evolution in subjects belonging to selected local native communities (Inuit citizens)6.

However, episodes of BCG-itis with thoracic and in particular respiratory, simii-tubercular localization have been reported with an extremely low frequency by the international literature8,19,21,22, while the cases of pulmonary-extrapulmonary tuberculosis caused by M. tuberculosis and occurring despite prior BCG vaccination are not so infrequent, so that the overall effectiveness of BCG vaccination remains under discussion20.

Among the extremely rare episodes of BCG-induced pulmonary tuberculosis, a careful literature search shows: one episode in a patient with a malignant hematological disease who underwent a prolonged immunosuppressive treatment with alemtuzumab19, an anecdotical case of systemic, lethal BCG-itis in a 18-year-old patient with a primary immunodeficiency, who also experienced a respiratory localization18, one episode of pulmonary and disseminated BCG disease occurred just in a patient treated with intravesical BCG instillations20, and a second case of granulomatous BCG pneumonia diagnosed after several cycles of local BCG therapy of an urothelial bladder carcinoma20, leading the published episodes to a global number of four cases only18,19,21,22, two of them caused by intravesical BCG administration21,22, as occurred in both our patients.

As a consequence, a respiratory BCG infection, especially when isolated, represents an extremely infrequent occurrence, burdened by a very cumbersome differential diagnosis, especially when the involved patients are affected by concomitant chronic respiratory disorders (i.e. COPD), or suffered from a prior lung tuberculosis (as in both cases reported by ours), or when immunodeficiency-related conditions or a severe general wasting caused by underlying illnesses are of concern. In all these circumstances, the BCG invasiveness is greater, whereas a rapid recognition and a timely differential diagnosis and specific treatment may be delayed.

When focusing our attention on the therapeutic use of BCG in the local management strategies of superficial, urothelial carcinoma of the bladder, an extensive study performed by Lamm et al. in the year 199221, for the first time faced systematically the untoward events following BCG instillation in a population of even 2,602 treated patients. In the 95% of reported BCG courses, fever and malaise were commonly registered in the days immediately following BCG therapy.

Severe BCG complications regarded a minority of cases. With regard to the genito-urinary distic, a granulomatous prostatitis occurred in 0.9% of treated patients21 (while no cases of penile localization occurred, as compared with the second case of ours), while long-distance localizations proved extremely rare: a pneumonia or a granulomatous hepatitis were recognized in 0.7% of overall examined patients (only one case of BCG pneumonia was reported), while a BCG sepsis and disseminated infection was an extremely rare occurrence (0.4% frequency)21.

In the year 1997, Allouc et al.23 reported their series which included 148 urologic patients who received local BCG due...
to a relapsing superficial bladder carcinoma, followed for a mean period of 40 months. Local, intravesical, and/or follicular reactions were detected in 46% of cases, but they had a favorable prognosis, since only slightly more than 10% of episodes required a specific anti-tubercular treatment. Of interest in relationship with both our case reports, the authors observed that the BCG complications which involved these cancer patients were significantly more frequent when a prior tuberculosis was recognized (on either clinical or especially imaging basis) (up to 50% of cases), when compared with patients with a negative clinical history and chest imaging of a previous tubercular illness 13.8% of cases only.

From a pathogenetic point of view, also reliable animal models have demonstrated that the exposure to mycobacterial antigens (including those of M. bovis), may exacerbate the clinical expression of a pulmonary M. tuberculosis disease (and mycobacterial diseases as a whole), due to the demonstrated immune activation mechanisms which increase the respiratory inflammation process via the secretion of large amounts of TNF-alpha and other proinflammatory cytokines, concurrently blunting most of defense mechanism, and the containment of local pulmonary mycobacterial load.

After the first relevant survey conducted on over 2,600 urologic cancer patients by Lamm et al., single case reports have been published in the international literature regarding anecdotal episodes of respiratory involvement (BCG pneumonia), granulomatous hepatitis, renal involvement (granulomatous nephritis), bone marrow invasion concurrent with liver disease, local ocular involvement (corioretinitis), and also vascular damage, mostly represented by aneurismatic lesions (of either native or prothertic large vessels), in one single episode associated with vertebral osteomyelitis, too. Finally, secondary to the local (intravesical) BCG administration, also isolated episodes of severe sepsis and disseminated BCG infection occurred anecdotally.

From a practical point of view, when BCG preparations are used as a local adjuvant therapy (mostly repeated cycles of endovesical instillation), these attenuated mycobacteria may gain access to the local hematic-lymphatic vessels, and subsequently have a systemic dissemination, in rare (but not impossible) occurrences. Although infrequently, these events may find a support when uroepithelial lesions are present (as happens in subjects treated for a bladder carcinoma with either surgery or chemotherapy), and when a state of general immunosuppression or reduced defence favored by the underlying disease and its treatment (either surgical, invasive, or cytotoxic ones), are of concern. When these subjects treated with local BCG instillations develop a local, distant, or disseminated inflammatory process, which sometimes may start with an apparently isolated fever and in absence of organ-site signs-symptoms, and it is refractory to an empirical wide-spectrum antimicrobial chemotherapy, an organ or disseminated BCG infection (although rare), should be always considered. As anticipated, particular attention should be deserved to subjects with a history of tuberculosis (as happened in both our patients), since they seem to have a greater risk to develop mycobacterial disease related to BCG administration. In fact, also physicians’ and patients’ informations included in the drug package commercialized in Italy, in its 2007 update, underline that “…patients must alert their physician as soon as possible when a worsening or a persistance of pre-existing signs and symptoms occurs, and also when one of these symptoms becomes evident, including cough. A persisting cough after vesical BCG instillation might be a sign of a severe BCG infection; should a BCG infection is confirmed, an immediate treatment with appropriate anti-tubercular drugs is needed…”.

As to specific treatment options, the M. bovis strain contained in BCG preparations, proves in vitro susceptible to almost all available anti-tubercular compounds, save the relevant exceptions of pyrazinamide and some other agents expressing anti-mycobacterial activity, like some aminoglycosides and some fluoroquinolone derivatives. In the current clinical practice, a three-month long therapy conducted with at least two active drugs (i.e. rifampicin and isoniazid), tested effective in the majority of cases of local (urinary) BCG disease according to an extensive French experience, but in our patients the severe pulmonary localizations were overcome by an underlying COPD, while in the second presented case a concurrent penile BCG granulomatous lesion required up to 8-12 months of anti-tubercular treatment, which was well tolerated from a clinical-laboratory point of view.

When considering possible preventive measures in urologic patients, a recent randomized study conducted in France allowed to observe that the administration of the fluoroquinolone ofloxacin after every endovesical BCG instillation significantly reduced the most severe and the systemic complications linked to this adjuvant therapy; unfortunately, no other literature evidences are present, to support this procedure.

In the particular case reports observed by us, both patients had concurrent radiological (HRCT) sequelae of a prior pulmonary tuberculosis, and both subjects were also affected by a long-lasting COPD (with a severe emphysematous-bulbous evolution in the second case), which made the recognition of a pulmonary BCG-itis characterized by an extensive miliary or interstitial-nodular involvement, more difficult. The histopathological studies pointed out a granulomatous-necrotizing nodular-epithelioid pneumonia with diffuse macrophage, histiocyte, and giant cell infiltration, followed in the second patient by endoalveolar fibrotic organization. In both patient, the BAL examination demonstrated a prevalence of lymphoid cells, histiocytes, reactive bronchial cells, and cylindromform cells of bronchial epithelium, in the apparent absence of mycobacteria at both microscopic and culture examinations.

At a moderately positive Mantoux intradermal reaction (first case) and a negative Mantoux testing (second case), were added a positive in vitro T-Lymphocyte testing (Quantiferon) in the first reported case, and an elevated, positive specific serodiagnosis for mycobacteriosis in the second patient, according to the available laboratory testing in that period (year 2001). With regard to the positive interferon-gamma-release assay (IGRA) of our first patient, we underline that our case report is the first one with a BCG-related organ complication.
diagnosed with the contribution of such a laboratory testing, to the best of our literature knowledge.

With regard to the clinical course and outcome, in both our cases the miliary and nodular-infiltrative picture of the first patient, and the granulomatous-fibrosant evolution of the second patient, had a slowly progressive clinical and imaging amelioration thanks to the well-tolerated associated anti-tubercular therapy, although the follow-up time of our first patient is limited to two months, compared with the more prolonged observation time of the second patient of ours. In this last patient, no residual infiltrates were present at HRCT control after one year, but functional lung examinations showed evident abnormalities especially under physical exercise, which represented a permanent sequela of the BCG pneumonia, since they remained unchanged after a six-year follow-up.

When discussing the potential pathogenetic links between intravesical BCG immunotherapy and BCG disease with pulmonary and pulmonary-genitourinary localization (in the first and in the second patient, respectively), after the careful exclusion of other etiologies no doubt can raise, although a respiratory localization mimicking tuberculosis (a miliary form in the first case), have been described very infrequently. After a careful revision of international literature, we found only four episodes of respiratory disease induced by BCG, two of them apparently caused by local BCG immunotherapy of urothelial bladder carcinoma. As a consequence, our case reports represent the fifth and the sixth absolute described cases of pulmonary BCG-it is observed until now, and the third and fourth absolute episodes following BCG instillation as adjuvant, local therapy of a relapsing bladder carcinoma. Furthermore, the penile granulomatous BCG lesion makes our second reported case unique, since in this last patient the BCG-it is following local immuno therapy interested another distant site with a localized granulomatous involvement, other than the respiratory one.

When assessing the pathogenetic mechanisms which relate the local BCG immunotherapy with an eventual occurrence of tuberculosis-like localizations, we have to remind that BCG preparations are based on attenuated M. bovis strains, which have lost most of their virulence, but still remain alive microorganisms. Interestingly, a localized and/or systemic BCG-it is may be not necessarily linked to a massive, direct mycobacterial infection, but it usually depends on an exceedingly elevated hypersensitivity reaction to a gross mycobacterial antigenic load: this perspective may also explain the frequent difficulty to retrieve BCG strains from pathological lesions by current microbiological techniques (i.e. microscopy and culture search), as happened in both our case reports. In the particular circumstance of neoplastic patients who underwent repeated local BCG instillation through invasive local interventions (i.e. cistoscopy, bladder catheterization), or during or after cytotoxic chemotherapy with secondary mucosal lesions, all these conditions may contribute to a hypersensitization against BCG antigens (beyond the possible hematogenous and/or lymphatic dissemination, as happens in the spontaneous military disease). Anyway, the massive mycobacterial antigen load, may lead per se to the formation of the characteristic giant-cell tubercular granulomas also in distant organs and sites, especially should a prior tuberculosis has been suffered in the past.

As anticipated, local-regional adverse reactions to BCG vaccine used to prevent tuberculosis in endemic areas or among exposed subjects, are proportionally common also in otherwise healthy people of each age, while a systemic involvement including hyperpyrexia, severe cough, respiratory distress, hemodynamic imbalance and mental status disturbances strongly suggest a pulmonary and/or disseminated BCG disease, which needs an elevated clinical suspicion for a prompt recognition, a rapid diagnostic confirmation, and a tempestive and prolonged association anti-tubercular therapy, with the preliminary workout to be realized preferably under a hospitalization regimen.

At the start of the third millennium, given the limits of efficacy and the non-negligible risks related to the continued use of BCG in the general population (as a vaccine), and in selected patients (i.e. adjuvant immunotherapy of bladder carcinoma), the need to prosecute research projects which may lead to the development of novel vaccines for the prevention of tuberculosis (an emerging and re-emerging disease in the last years, also in industrialized countries), become more and more warranted. More immunogenic compounds, improved protection against tuberculosis and ameliorated clinical efficacy as an adjuvant therapy, and especially more safe preparations when compared with standard BCG preparations (used since over 70 years), are strongly needed.

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