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EDITORIAL

NEW HOPES IN PD-1 IMMUNOTHERAPY FOR CANCER

PD-1 (Programmed Death-1) immune regulatory receptor was discovered by Honjo *et al* in 1992.[1] It plays a critical role in auto-immunity, infections transplantation, allergy and block immunotherapy.[2,3] PD-1 acts through inhibition of T-cells during long term exposure to antigens such as those effected by viruses or tumors.

In the past, immunotherapy had generally exploited three basic concepts, firstly potentiation of the immune system by immuno-stimulants (e.g. interferon or interleukins), secondly by vaccines using dendritic-cell based, inactivated tumor components, since dendritic cells play a central role in directing T-cell response to cancer and, thirdly intra-tumor bacterial injection to induce inflammation and antitumor effect. Antecedent modes of this sort had low response rates in tumors like melanoma and renal cell carcinoma but in the face of serious toxic effects. Moreover, such approaches could not overcome tumor escape mechanisms from immune responses by T-cells.

CTLA-4 or PD-1 is expressed about 48 hours after T-cell activation, providing negative signaling. CTL-4 can be antagonized by blocking antibodies such as ipilimumab and tremelimumab and resultant objective responses in 10-15% of metastatic melanoma associated with autoimmune toxicity and inflammation in double those percentages.[4] PD-1 receptor is another inhibitory T-cell receptor with two ligands PD-L1 and PD-L2 occurring within tumor microenvironment. [4,5,6] Inhibition of PD-1, in fact, sustains fewer side effects and greater antitumor activity than CTL-4.

Two initial trials employing Anti-PD-1 antibodies[7,8] provided reference points as to the effectiveness of Anti-PD-1 antibodies in producing response rates of 10-15% in melanoma and renal cell carcinoma, whereby such mode of immunotherapy is active at the molecular levels and providing targeting or personalized therapy, knowing that such treatment can be selected in patients who carry the receptor revealed through immunohisto-chemical testing of paraffin sections of tumors of interest. This area of research raises hopes for designing therapeutic regimens within immune-modulating or inhibiting agents which can predict response in individual cases. Long term response resulting from use of PD-1 inhibitors is very encouraging. Long term effect of such agents may come about through recruitment of memory T-cells from the immune system. PD-1 blockage has two advantages: one is reduced toxic effect and the other enabling patient selectivity for better tumor response. We have to await more convincing studies and results in this direction.

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The Editor

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Disseminated BCG Following Intra-vesical Therapy for Transitional Cell Carcinoma, Report of Two Cases

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Introduction

Intravesical vaccination by BCG has proved to be an effective immunotherapy of superficial transitional cell carcinoma (TCC) of the urinary bladder. It is useful in slowing down of the tumour progression and improves patients' survival.[1] Its side effects include local urinary symptoms and mild general side effects. Serious systemic complications of intravesical BCG immunotherapy are rare. [2] We describe two patients who developed dissemination of BCG following intravesical instillation for the treatment of bladder TCC.

Cases and Results

Patient 1, aged 70 years had resection of bladder G3 pTa TCC in October 2010 which recurred and resected again in December 2010. There was no residual tumour seen on cystoscopy in May 2011 and bladder biopsy was negative for carcinoma. Intravesical BCG vaccination was carried out in July 2011. Check cystoscopy, one month later showed erythema of bladder mucosa and no recurrent carcinoma which was proven on bladder biopsy. Patient started to develop spiking temperature and drop in lung function in October 2011. Blood tests showed WBCs of 5.3x109/ Litre, RBCs of 3.75x1012/Litre, Hb of 12.2g/dl, and low platelets of 30x109/Litre. A presumptive diagnosis of idiopathic thrombocytopenic purpura was made. Therefore, bone marrow aspirate and trephine were taken. Chest x-ray of this patient showed lung shadowing suggestive of tuberculosis. Bone marrow trephine biopsies contained multiple well formed epithelioid cell granulomas without caseation. Zeihl-Neelson stains for acid- fast bacilli were negative. Blood and urine cultures were negative. Blood biochemistry tests, as serum electrolytes, liver and kidney function tests were within normal limits. The diagnosis of disseminated BCG was established and the patient were treated promptly with antituberculous therapy including steroid and have been cured.

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Disseminated BCG

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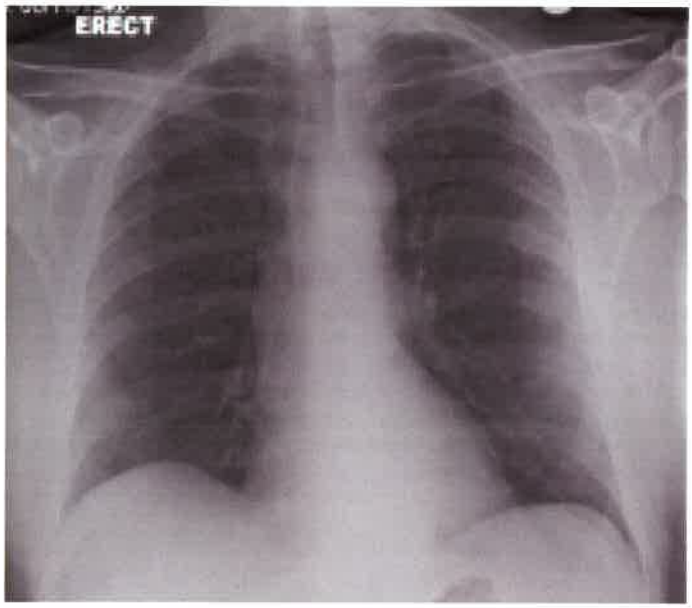

Figure 1. Case 1: Lung shadowing.

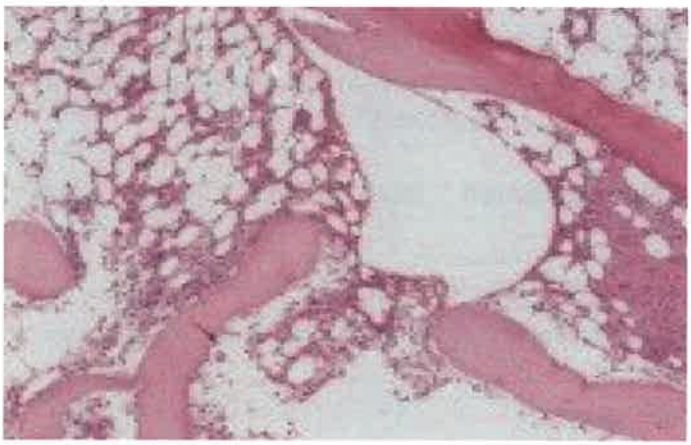

Figure 2. (X10) Case 1. Bone marrow with granulomas.

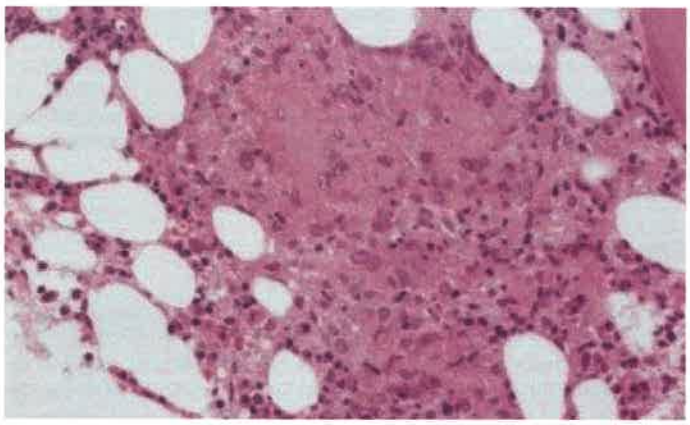

Figure 3. (X40) Case 1. Epithelioid granuloma in bone marrow.

Patient 2, aged 78 years who was referred to Haematology services for fever, weight loss, difficult breathing and anemia. His blood tests showed: WBCs of 6.9x109/Litre, RBCs of $3.4x10^{12}$/Litre, Hb of 10.1g/dl and Platelet Count of $237x10^{9}$/Litre. He was investigated by examination of bone marrow aspirate and trephine biopsies. Bone marrow trephine biopsies contained multiple well formed epithelioid cell granulomas without caseation. Acid- Fast bacilli special stains (Zihl-Neelson) were negative. Blood and urine cultures were negative. The patient was noted to have developed TCC of bladder which has been diagnosed somewhere. This TCC has been treated by biopsy resection and BCG vaccination of the bladder mucosa 3 months earlier. Chest x-ray displayed subtle lung nodules; these were confirmed on chest CT scans as consistent with pulmonary tuberculosis. The diagnosis of disseminated BCG was established. The patient was treated promptly with antituberculous therapy including steroid and have been cured.

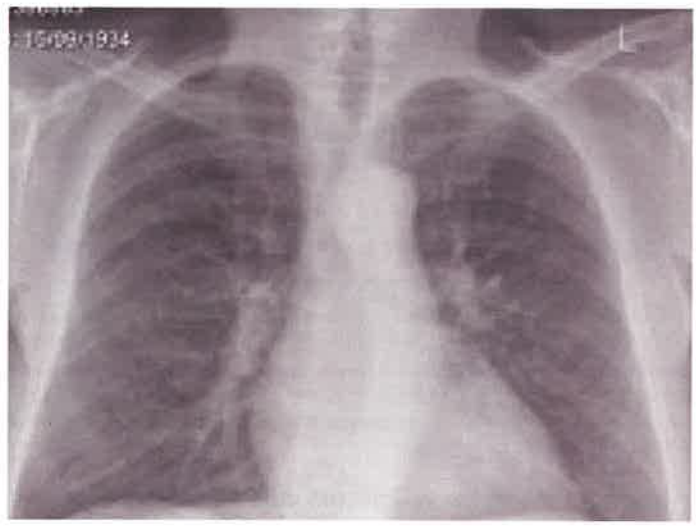

Figure 4. Case 2: Nodules in lungs.

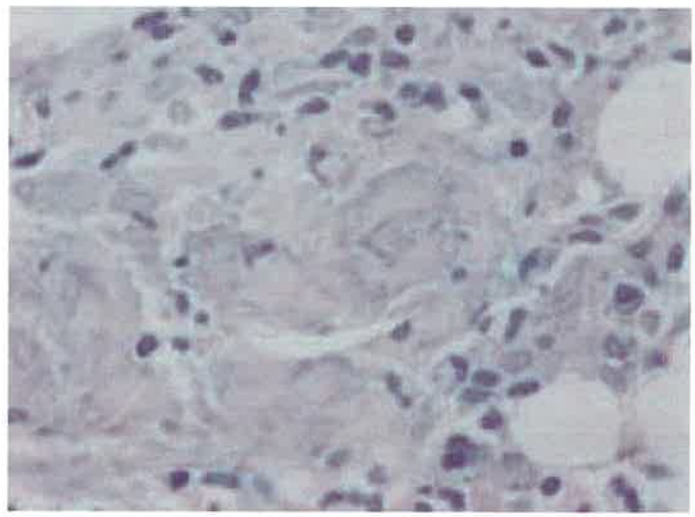

Figure 5. Case 2: Bone marrow granuloma.

Discussion

The chance of developing transitional cell carcinoma (TCC) is on the increase in the steadily ageing population and many of these cases would be treated by BCG vaccination to the bladder mucosa. At same time, many of these patients are expected to have age related immunosuppression or other disease-related or therapy-related immunocompromising conditions. Consequently, they become more susceptible to development of disseminated BCG.[3,4]

Medline search showed only two case reports of disseminated BCG from the UK; one case presented with cutaneous lesions (Ng et al, 2006)[5] and the other with mycotic aortic aneurysm (Maundrell et al, 2011).[6] No cases of bone marrow involvement have been described in the UK.

Lamm and colleagues (1992) have estimated that 0.1% of BCG vaccine recipients for bladder carcinoma to develop bone marrow involvement and pancytopenia. Only 11 cases of bone marrow involvement by disseminated BCG have been described from Europe (other than UK) and North America until 2009.[7,8] We, therefore, are reporting the first two cases of disseminated BCG with bone marrow involvement in the UK.

The mechanism of what is called "BCG-itis" is unclear yet; it may be due to a systemic delayed-hypersensitivity reaction. This is supported by the effective response of patient's symptoms to steroid treatment. On other hand, direct seeding of bacteria via haematogenous route is thought to be the culprit.[9,10] Several factors like traumatic instillation, concurrent cystitis and disturbed mucosal integrity by simultaneous

(Continued on page 3)

Disseminated BCG

(Continued from page 2)

biopsy or transurethral resection of tumor caused the dissemination of viable attenuated organism of BCG vaccine. As the hypersensitivity and infectious mechanisms cannot be differentiated histologically and clinically, the recommended first line therapy for disseminated BCG is the administration of isoniazid, rifampin and ethambutol for three to six months together with corticosteroids therapy.

Ziehl-Neelson staining for acid-fast bacilli in tissue sections and conventional mycobacterial culture are inadequate methods for the identification of the BCG bacilli (mycobacterium bovis). This could be related to the paucity of organisms in the affected site and therefore molecular assays may have superior sensitivity to traditional methods.

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ON MEDICOLEGAL ISSUES

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The medical profession is considered one of the noblest human careers. For that, medical practitioners need a great deal of freedom, trust and ease at work to enable them to do their job without fear or hesitation. A patient's life and body safety remain the most precious among social values that need protection. Human rights are the most valuable among all rights. Science and technological advances pose, day after day, new risks to modern medical practice that burden medical practitioners, requiring them to be aware of any new innovations and their accompanying features, including new risks or side effects on health, requiring a balance between advantages and hazards entailed and which should be explained to those receiving such new therapies. This involves use of new instruments and technologies that require highly specialized training in the working of such instruments and whose role becomes essential to the success of the medical therapist in the use of modern therapeutic modalities.

Jordan has encountered in the last two decades a great advance in medical technology, during which time new hazards have emerged to medical practice, especially after increased role of medical engineering in medical practice and its engagement in certain subspecialties, diagnostic and therapeutic alike. In this context, there appeared problems relating to morbidity and mortality arising from accidents caused by new technological and therapeutic modalities. Such accidents have associated with an increase in the number of lawsuit cases against medical practitioners filing for compensations against damages, whether physical or material. Such trend was probably driven by increased awareness of the public and active participation of lawyers on such issues. Patients are often not convinced that fate alone is responsible for medical mistakes incurred upon patients under medical care. In reviewing a number of cases, such mistakes were made by lack of experience, knowledge or negligence. And although it is self-evident that justice should compensate against any wrong doing, achieving this is not so easy. Laws stipulate that any felony or otherwise should be supported by proof of wrong doing by the treating physician , with evidence needs to be established by patients and their counsel, or otherwise any claims will bounce. Physicians are usually accounted for their wrong doings on their patients without differentiation whether if this wrong doing is serious or not, the only requirement is for the wrong doing to be evident. This, of course is not entirely logical. There are evidently cases which are recognized as a known complication of risk and in many cases would have been explained to the patient before embarking on management in question.

Nevetheless, physicians remain responsible for any negligence of any degree according to common medical concepts based on traditional and subjective standards. Therefore, we find it timely to initiate evaluation of medical malpractice in a practical manner through quantitative study, situation analysis, thereafter reviewing verdicts through critical appraisal approach. A pilot study was conducted by collecting cases from higher cassation courts concluded by a judicial system in Jordan, Kuwait, Lebanon and France, to allow more indepth comparative studies in the future . In reference to judicial jurisprudence in the field of medical responsibility it was revealed that the common medical negligence usually leads to liability and requires compensation in contrast to some lesser cases that might lead to criminal actions.

Examples of civil medical malpractice: Refusal of providing *treatment*, wrong *diagnosis* or wrong doing in *surgery, plastic surgery, obstetrics, x-ray and radiology,* public governmental and private *hospitals.*

Further communications will address health care service providers to develop their work within legislative and ethical framework in our country and achieve better quality practice. This will require clear and peer reviewed ethics standards and guidelines. Subjects of interest will include:

1. Informed consent especially minors and donations dealing with senile and mentally ill people, together with, consent taken from youngsters between 15-18 years of age.
2. Dealing with all cases of violence especially underage and cases of injuries furnishing medico-legal reports.
3. Secrecy versus reporting and divulging medical information.
4. Problematic issues in dealing with termination of pregnancy whether due to disease or psychological problems or unwanted pregnancies this might extend to establish clear guidelines to deal with IVF cases and will dealing destroying excess cells.
5. Informed discharge
6. Guidelines dealing with terminally ill patients and those who don't want to receive resuscitations anymore (DNR).

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Birthplace & Childhood

I was born in Dair Al Ghusoun in Tulkarm in Palestine (later West Bank), on the 18th of August 1932. I attended Tulkarm Elementary and Secondary Schools from 1939 to 1950, after which I passed the Palestine Matriculation in June 1950.

University Education

In 1950, my father decided to send me to Lebanon for studying at the American University of Beirut. I spent two years there, but in 1952, when I heard that the Jordanian Armed Forces commenced recruiting high school graduates for scholarships to medical schools in England, I left Beirut to Amman, applied and was accepted to do medicine in England. During that same year, I enrolled in the Northern Polytechnic in London for a two-year course leading to Advanced Level G.C.E (General Certificate of Education). On obtaining the necessary qualification, I entered medical school at King's College, London and King's College Hospital where I spent a 5-year period, from 1954 till 1959, obtaining LRCP (London) and MRCS (England) in April 1959 and M.B, B.S. (University of London). In May 1959, I returned to Jordan and worked as a military doctor and officer in the Jordanian Army.

Specialization

I was sent again to England by the Army to specialize in Radiology where I became a trainee in Diagnostic Radiology at King's College Hospital, London from October 1963 until October 1965 at the end of which I passed the DMRD Examination.
I became a Specialist in Diagnostic Radiology at the Army Base Hospital in Marka from January 1966 to May 1970, then travelled to England once again to work as an Honorary Senior Registrar at King's College Hospital for 7 months. Thereafter, I passed the FFR Examination, following which I became Visitor to specialized Hospitals in London from Dec 1970 to March 1971. Later, I traveled to Canada and worked as locum Consultant Radiologist for 6 weeks.
I came back to Jordan and worked as Senior Specialist at the Army Base Hospital, Marka for 2 years, then was sent back to England to sub-specialize in Neuro-radiology at the National Hospital for Nervous Diseases in London for one year.

Career stops

I was appointed Director of Radiology Department at the Army Base Hospital from August 1967 until August 1973. After that, when King Hussein Medical Center opened, I became Director of Radiology Department there from August 1973 to October 1994.
During this period of time, I was assigned other administrative posts including Chief of Administrative Services, then Chief of Professional Services at the Royal Medical Services, General Director of King Hussein Medical Center and Chief of Professional Services at The National Medical Institution.
After retiring from the Army, I worked as Director of Radiology Department at the Arab Medical Center, Amman from November 1994 until I retired in 2006.
During my working career, I was involved in delivering many lectures and seminars to doctors at the Royal Medical Services, Jordan University Hospital and the Jordan Medical Association. I was awarded the title of Clinical Professor in Clinical Radiology at the Jordan University of Science And Technology in 1992.
I served as President of the Jordanian Radiologic Society (1986-1988 and 1995-1997, respectively)

Family set-up

I am happily married to Hiam Qassim since 1961.
My wife had worked as a teacher at the UNRWA School in Amman. She later gave up work to very lovingly take care of our growing family. I have 3 children: Lana, Luma and Tariq.

Hobbies

My hobbies are swimming and walking.

People who impressed and left an influence on me: A great teacher who left his marks on me was the late Dr Laws, a British radiologist. He was my mentor when I was specializing in radiology. He was impressed and happy to see a hard working doctor from our part of the world who was as good as his British colleagues. He took special care of me and taught me almost everything I know with great enthusiasm. He spent many hours showing me all kinds of radiology cases and leaving me to make the diagnoses. He even preferentially recommended me for the Locum job in Canada over the rest of my colleagues. I was deeply saddened when I learned that he had passed away. I can never repay him enough for all he had done for me.
Words of advice to future medical graduates: My advice to the young medical generation is to be ambitious, work hard and be loyal in whatever you choose to continue your career in and maintain a high level of professionalism . Keep up to date with all the new medical information, and be open minded in your discussions and in accepting the ongoing changes in the medical profession.

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Gardenia on a dish.