

LETTERS TO THE EDITOR

## Unusual clinical features of cutaneous tuberculosis in a patient with myelodysplastic syndrome: Late complication of intravesical instillation of Bacillus Calmette-Guérin vaccine

Dear Editor,

Cutaneous tuberculosis (CTB) is uncommon, comprising 1-1.5% of all extra-pulmonary tuberculosis manifestations [1]. A more accurate classification of CTB includes inoculation tuberculosis, tuberculosis from an endogenous source and haematogenous tuberculosis. The lesions caused by mycobacterium species vary from small papules (e.g. primary inoculation tuberculosis) and warty lesions (e.g. tuberculosis verrucosa cutis) to massive ulcers (e.g. Buruli ulcer) and plaques (e.g. lupus vulgaris) that can be highly deformative [1].

Herein we present a 67-year-old man who complained for pain, swelling, oedema and erythema of right ear and cheek. These changes occurred few months before admission (December 2014) and became more pronounced over time. There were no systemic complaints. The patient had an 8-month history of myelodysplastic syndrome (MDS), refractory anaemia with excess of blasts type 2 (RAEB-2) with normal karyotype (46,XY) and 5-year history of superficial bladder cancer. Since he refused chemotherapy, treatment of his MDS consisted of supportive therapy. Bladder cancer was treated surgically (transurethral resection of the tumor was performed on 4 occasions), in addition with intravesical instillation of bacillus Calmette-Guérin (BCG) vaccine as adjunctive therapy (6 times, last time in November 2010). On admission, physical examination showed infiltrating circumscribed erythematous plaques with bumpy surface in the region of the right ear and cheek, involving eyelids (Figure 1). At first he was examined by dermatologists as non specific granulomatous inflammatory skin disease with no clinical

response to topical corticosteroid therapy. Histology of the skin lesions demonstrated chronic inflammatory changes with multinucleated giant cells and noncaseating granulomas and positive Ziehl-Neelsen staining. Sputum on Lowenstein was negative 3 times, but QuantiFERON-TB Gold test was positive. Computed tomography of the thorax showed presence of fibrotic changes in the upper parts of the lung, presumably as a result of an old specific process. Antituberculosis therapy consisted of isoniazid, rifampicin, ethambutol and pyrazinamide during the first 2 months, and rifampicin and ethambutol for next 4 months. After 6 months of antituberculosis therapy, cutaneous infiltrations on the face and ears regressed completely (Figure 1). However, 3 months later the patient died due to transformation of MDS into acute myeloid leukemia.

To our knowledge, this patient is the first reported case of BCGitis in patients with MDS. Namely, tuberculosis can be early or late complication of intravesical instillation of BCG [2]. Late presentation of disease occurs >1 year after the first BCG treatment, sometimes years after the last instillation which may hinder prompt diagnosis and treatment. It usually involves focal infection of the genitourinary tract (the site at which bacteria were introduced) and/or other sites that are typical for reactivation of mycobacterial disease, such as the vertebral spine, but rarely elsewhere [2]. Noncaseating granulomas are found in the majority of cases [3] as is the case in our patient. Exclusion of other entities and the prompt response to antituberculosis treatment should be considered the cornerstones of diagnosis of BCG infection since cultures often remain negative.



**Figure 1.** Cutaneous lesions at presentation (left) and after 6 months of antituberculosis therapy (right).

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## Is switching to tamoxifen the only choice of treatment for improving aromatase inhibitor toxicity?

Dear Editor,

Despite the excellent disease outcomes with anti-endocrine therapy, 20% of patients will not continue with aromatase inhibitors (AI) therapy, primarily due to the toxicity of treatment. Kwan and colleagues [1] investigated patterns and reasons for switching classes of hormonal therapy among 3,265 women with early-stage breast cancer. There were 290 women who switched from AI to tamoxifen (TAM) (AI switchers), including 130 (45%) switchers during the first year of treatment. Associated with this, Henry et al. [2] evaluated the associations between patient and anthropometric characteristics and AI discontinuation and reported that 40.9% of 93 AI-treated patients discontinued endocrine therapy within 12 months because of toxicity, a finding similar to what has been reported in the current study by Kwan et al [1]. In clinical practice, we have to find some challenges in improving the toxicity of AI and it is common practice to switch to TAM in these patients. I want to add some possible alternative treatment choices as well. If the patient does not tolerate the first AI medication as steroidal or non-steroidal AIs, it would be rational to switch to non-steroidal or steroidal AIs, respectively. Secondly, the

first AI medication might be given every other day. Thirdly, intermittent discontinuation of AI might be another choice. However, these treatment alternatives should be validated in prospective studies.

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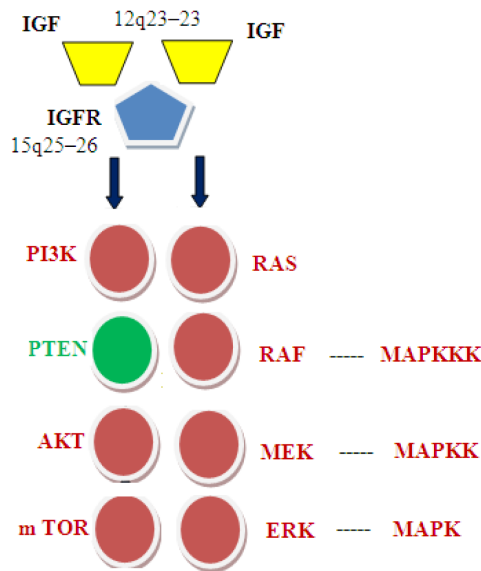
## IGF/IGFR and diabetes mellitus in head and neck squamous cell carcinoma patients

Dear Editor,

Deregulation in metabolism is a serious issue regarding patients suffering from cancer. Concerning Head and Neck Squamous Cell Carcinomas (HNSCC), alterations in growth factor receptors combined with the corresponding ligands negatively influence prognosis and response rates to chemo-radio therapeutic regimens. The human Insulin-like growth factor receptor type 1 (IGFR-1) gene on chromosome 15q25-26 encodes for a protein which is expressed by almost all tissues and cell types during embryogenesis. Activation of the receptor is mediated by ligand-binding of Insulin-like growth factor 1 (IGF-1), also

called somatomedin C (gene on chromosome 12q23-23) [1]. IGF molecules form complexes with six binding proteins (IGFBPs) in the plasma, but free IGFs are responsible for inducing Ras/Raf/MEK and PI3K/AKT/PTEN/mTOR up-regulation by amplifying the signal transduction (Figure 1). The result is a cascade of intracellular reactions deregulating crucial for cell growth, proliferation, survival and cell cycle gene functions [2]. In fact, IGF-1 acts as hormone similar in molecular structure to insulin demonstrating anabolic effects. The role of its altered expression in patients with HNSCC, especially combined with presence of absence of human papillomavirus (HPV), is under investigation. A study group recently showed that IGF-1R

expression is associated with HPV-negative status and adverse survival in these patients [3]. They also observed that IGF-1R was independently associated with survival in multivariate analysis. They proposed that treatment based on anti-IGF-1R agents should be a much challenged approach for handling subgroups of patients characterized by specific pathology (ie HPV-negative and high IGF-1R HPV-positive).



**Figure 1.** IGF/IGFR complex depended signaling transduction pathways (Ras/Raf/MEK and PI3K/AKT/PTEN/mTOR). Red spots: oncogenes, Green spot: suppressor gene, Blue trapezoid: Growth factor receptor, Yellow trapezoid: Receptor's ligand

Diabetes mellitus (DM) seems to be associated with some cancers. A recently published study showed that the risk of developing HNSCC was decreased among diabetic patients compared to non-diabetic ones [4]. Interestingly, this risk was further decreased among diabetic metformin users even they were current smokers or exposed to chronic alcohol consumption. It is known that metformin is an oral anti-hyperglycemic agent used to treat type 2 DM. In conjunction with the previous results, another study group concluded that metformin prevents the progression of dysplastic mucosa even in non-diabetic patients [5]. They analyzed the results of adjuvant metformin therapy for treating recurrent and multifocal dysplastic lesions in pre-

viously treated non-diabetic HNSCC patients. Interestingly, all examined cases showed complete or partial regression of the remaining mucosal lesions and did not require any additional operations. Understanding the mechanisms of IGF/IGFR deregulation in HNSCC is a promising field in molecular-based handling of these patients. Furthermore, the preventing role of specific antidiabetic agents, such as metformin, in the development and progression of the current malignancy seems to be crucial even in non-type 2 DM patients. The last earn benefits of resistance in the carcinogenetic process even demonstrating dysplastic squamous cell mucosa, evidence that this drug acts as a suppressor agent in cell proliferation.

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## Do systemic recurrences increase after the use of scalp cooling in patients treated for breast cancer with chemotherapy?

Dear Editor,

Alopecia is a common side effect of almost all effective chemotherapy regimens in breast cancer. Scalp cooling is used to prevent chemotherapy-induced alopecia. The protection from alopecia by scalp cooling is known to be due to both vasoconstriction resulting in reduced blood flow

in the scalp, and reduced metabolic rate in the hair follicles. The primary concern that has limited the use of scalp cooling devices is the possibility that scalp cooling could increase the risk for scalp metastases. Rugo and colleagues [1] evaluated the effect of scalp cooling versus no scalp cooling on the risk of scalp metastasis in patients treated for breast cancer with chemotherapy. Their systematic re-

view and meta-analysis suggested that scalp cooling does not increase the incidence of scalp metastases. Two recent articles evaluated the use of scalp cooling in women with early-stage breast cancer receiving certain types of chemotherapy. In both studies, scalp cooling was associated with less hair loss [2,3]. However, a common problematic issue in scalp cooling during chemotherapy may be the concern of increased systemic recurrence rather than concentrating on the incidence of scalp metastases. Scalp cooling, in addition to leading to less hair loss in early-stage breast cancer patients receiving chemotherapy, may also protect circulating tumor cells (CTCs) which are the source of systemic recurrence through vasoconstriction resulting in reduced blood flow and reduced metabolic rate in the scalp [4]. Protected CTCs may disseminate to other common metastatic sites in breast cancer patients. Taken all together, long-term survival data are needed to validate comfortable use of scalp cooling especially in high risk early-breast cancer patients.

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# The struggle for intensive care coverage of patients with hepatobiliary malignancies in Greece: Patients are not numbers

Dear Editor,

We read with interest the correspondence by Sotiropoulos et al. [1], highlighting the contentious challenge of the scarcity of intensive care unit (ICU) availability in Greek hospitals. Intensive Care Coverage shortage is a challenging reality that Healthcare Systems face worldwide due to greater demand arising from the complexity of medical procedures or diseases but also the increasing patient age and expectations [2].

Sotiropoulos et al. identified several risk factors for ICU need, supporting the concept of individualized preoperative evaluation that could enable operations to be done without ICU admission need. Of interest, the authors also reported a 130% increase in postoperative ICU admissions compared to preoperative assessment estimation. This misjudge could be attributed to intraoperative factors that increased the severity of the operation, but mainly due to the inadequacy of the preoperative predictive models to assess ICU admission risk.

The tenets of biomedical ethics indicate that protocols should be used to guide ICU allocation when demand exceeds availability [2]. But at the same time, no formal triage protocols are routinely used to decide patient ICU admission [2]. A systematic review reported that patients who are perceived not to benefit from critical care are more often refused ICU admission and the refusal is associated with an increased risk of in-hospital death [3]. Thus, the factors used for triage should be currently considered as of

uncertain relative significance.

The medical-philosophical basis of the Hippocratic tutorship, that is still alive in modern Greek medical service, consists of the harmonic relationship between the physician and the patient [4]. During the era of modern medicine, extrinsic factors, such as financial crisis, have deranged the patient-focused medicine [5], giving birth to strategies that would stratify patients according to their healthcare needs and prioritize their treatment based on rapidly changing, not well-established recommendations, rather than evidence-based guidelines. In order to meet the challenge, physicians should focus on following the established bioethical and medical guidelines. Patients are not numbers and no "discount" on individual treatment should be accepted, if a patient is eligible to such treatment. Moreover, informed consent to "suboptimal" treatment is not a panacea and should be used judiciously.

In conclusion, we would agree that current medicine in Greece should take into consideration the obstacles that financial crisis sets to its application. But the answer to this challenge should be the maintenance of high-quality, patient-centered medicine that offers each patient equal opportunities to best possible care according to current guidelines.

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## Risk factors for development of breast cancer in premenopausal women with atypical ductal hyperplasia are more complicated

Dear Editor,

Atypical ductal hyperplasia (ADH) is a benign breast lesion associated with a 24-47% incidence of breast cancer at 25 years. Eighty to ninety percent of these lesions are estrogen receptor positive. The mechanisms by which ADH lesions develop into cancer are not clearly known. Recently, Santen and his colleagues [1] investigated the levels of aromatase in ADH lesions, tissue surrounding the ADH, and in dense and non-dense normal breast tissue. They found that overexpression of aromatase in breast tissue and its resultant increase in estradiol levels may contribute to the later development of breast cancer in women with ADH. However, the authors selected only postmenopausal women with ADH in order to reduce possible heterogeneity. Many premenopausal patients with ADH exist and their aromatase expression with further development of breast cancer risk are of utmost interest. It may be speculated that since their ovarian function is active, breast cancer development risk may be more attributed to higher estrogen levels produced by the ovary. Associated with this, Brown et al. investigated the effect of menopause on breast aromatase expression in relation to body mass index (BMI), white adipose tissue inflammation (WATi) and systemic markers of metabolic dysfunction [2]. This cross-sectional study consisted of 102 premenopausal (aged 27-56) and 59 postmenopausal (aged 45-74) women who underwent mastectomy for breast cancer treatment/prevention (2010-2015). They reported that aromatase levels were higher in breast tissue of postmeno-

pausal women, compared with premenopausal women. Taken all together, breast cancer risk in premenopausal women with ADH is more complicated since more risk factors are expected, such as aromatase expression, higher expression level of estrogen attributed to functioning ovary, and high frequency of dense breast.

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## “The moon on the water”: a characteristic ultrasonographic appearance of testicular lymphoma

Dear Editor,

Primary testicular lymphoma is an extranodal lymphoma developing in the testis. It accounts only 1-2% of all non-Hodgkin's lymphomas and 1-7% of all testicular tumors [1]. Most of the patients are older than 50 years.

The prognosis of patients affected by this disease is poor, with the 5-year overall survival ranging between 70 and 80%. A 53-year-old male presented at our Department of Urology for a right testicular growth that created mild pain and discomfort for about 2 months. There were no fever, haematuria, dysuria or symptoms from the lower

urinary tract. His medical history was unremarkable and he denied ever being infected with a sexually transmitted disease or trauma. On physical examination, we found a non-tender mass in the right hemiscrotum. The overlying skin was completely intact with no erythema. The left testis was also normal. Examination revealed no signs of lymphadenopathy in the groin and a mild degree of varicocele on the left side. Blood pressure was 130/90 mmHg and temperature was 36.5°C. The patient did not demonstrate any laboratory signs of inflammation (white blood cells, C reactive protein). Other laboratory tests (complete blood count, prothrombin, partial thromboplastin, urinalysis) were within normal range. Serum levels of  $\beta$ -subunit human chorionic gonadotropin (HCG) and  $\alpha$ -fetoprotein (AFP) were also within normal range.

The ultrasonographic (US) study of the scrotum reported an enlarged right testis (55x38mm) with diffuse and focal hypoechoic homogeneous lesions, while the shape of the testis was normal. Moreover, a thickened scrotal wall and an inhomogeneous scrotal echo pattern, such as the small waves on the water surface, was observed. This US appearance of the testis was similar to the picture “the moon on the water” (Figure 1,2A). The US color-Doppler study of the scrotum showed increased vascularity of the right testis. The patient underwent right orchiectomy and histology showed a primary testicular diffuse large B-cell non-Hodgkin’s lymphoma confined within the tunica albuginea (T1N0M0). Chemotherapy and radiation to the contralateral testis and regional lymph nodes were carried out.

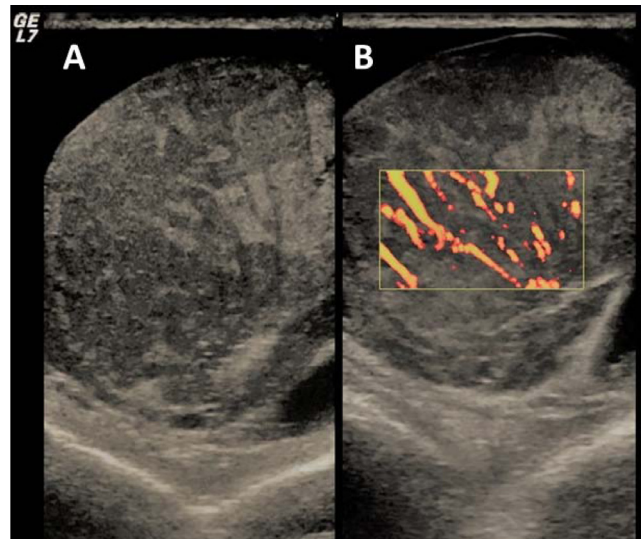
Testicular lymphoma generally presents as a painless testicular mass, and less commonly, with systemic symptoms such as fever, weakness and weight loss [2,3]. Tumor markers such as HCG and AFP are rarely elevated [4]. Its symptoms are non-specific and the differential diagnosis comprises testicular tumors, leukaemia, orchitis, sarcoidosis, tuberculosis and testicular abscess [1-4]. The US patterns of testicular lymphoma need to be differentiated from other testicular diseases [5]. We believe that our US findings contribute to the better knowledge of testicular imaging. A specific appearance of testicular lymphoma with focal and diffuse hypoechoic enlarged testis with hypervascularity as a “moon on the water”, can be described on testicular US. Ultrasound is also appropriate for the evaluation of inguinal lymph node chains [3]. However, the diagnosis requires histological confirmation [1-3].

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**Figure 1.** The full moon on water surface. Public domain image: (<https://it.pinterest.com/explore/moon-over-water/>).



**Figure 2.** (A) Sagittal gray-scale image shows enlarged, right testicle with diffuse and focal hypoechoic homogeneous lesions. Note the thickened scrotal wall and its inhomogeneous scrotal echo patterns, such as the full moon on the water surface. (B) Color-Doppler study reveals an increase in vascular flow.

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# The link between obesity and triple negative breast cancer

Dear Editor,

Obesity is associated with tumor promoting pathways related to insulin resistance and chronic low-grade inflammation which have been linked to various disease states, including cancer. The association between obesity and other breast cancer subtypes, such as triple-negative breast cancer (TNBC) and Her2/neu+ (Her2+) breast cancer, is less clear. Gershuni and his colleagues [1] evaluated the association between body mass index (BMI) and breast cancer subtypes in 848 patients diagnosed with primary operable breast cancer. They found that obese and overweight women were more likely to present with TNBC and normal weight women with Her2+ breast cancer. Associated with this, we investigated the association between BMI at presentation and breast cancer subtypes defined according to the immunohistochemical classification in 3767 breast cancer patients, both premenopausal and postmenopausal [2]. Triple-negative subtype was significantly more frequent in premenopausal patients with BMI  $\geq 30$  kg/m<sup>2</sup> compared to BMI  $< 30$  kg/m<sup>2</sup> (p=0.007). However, we did not notice significant association between triple-negative subtype and BMI in postmenopausal patients (p=0.862). Another previous study by Turkoz et al. also showed that premenopausal obese patients had an increased rate of hormone-negative breast cancer [3]. Similarly, Petekkaya et al. indicated a significant increase in ER/PR negative tumors among premenopausal breast cancer patients with

BMI  $\geq 25$  kg/m<sup>2</sup> [4]. Taken all together, association between obesity and TNBC may be better determined according to menopausal status of patients at the time of diagnosis.

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