

LETTERS TO THE EDITOR

Insomnia caused by aromatase inhibitors; a therapeutic challenge in patients with breast cancer

Dear Editor,

The use of aromatase inhibitors (AI) in the adjuvant setting of hormone receptor positive breast cancer patients are shown to have psychosomatic and menopause-like side effects. One of these psychosomatic side effects is insomnia, the complaint of inadequate or poor-quality sleep, which interferes and degrades breast cancer patients' quality of life.

Several studies with regard to this issue have demonstrated an increased incidence of insomnia associated with AI. However, in those studies, insomnia was attributed secondary to the well-known side effects of AI such as flushing and arthralgia [1,2]. However, in our patients we observed that the complaint of insomnia seemed to occur irrespective of other common side effects and occurred solitarily. In addition, it is well-defined that estrogens play an important role in sleep regulation and their deficiency can cause insomnia. Nevertheless, estrogen replacement therapy in postmenopausal women has been found to be ineffective in sleep problems [3]. To date, many studies have evaluated the effect of estrogens on sleep regulation in menopausal women and the results were inconsistent; while part of the studies reported an improvement in subjective sleep pattern in women receiving estrogens, others found either no effect or a degree of negative effect. These results relevant to insomnia caused by AI are confounding and apparently much more sophisticated than it is anticipated.

Diminishing estrogen levels due to AI can directly lead to insomnia. There has not yet been a consensus with respect to dose adjustment or interruption in case of insomnia which occurs during use of AI. Furthermore, there is also no recommendation or a specific therapeutic agent for preventing insomnia associated with AI. However, there is some evidence in the literature that behavio-

ral therapy may prevent insomnia in patients with breast cancer [4].

Although our primary aim in breast cancer patients is to provide a better survival outcome, improving patients' quality of life is also crucial and within our responsibility. Thereby, we emphasize in this Letter that probable pathophysiology of insomnia due to AI should be acknowledged and necessary precautions for preventing this clinical issue should be undertaken in consensus.

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Ductal component - need for personalized follow-up after radical prostatectomy

Dear Editor,

Ductal carcinoma of the prostate (DC-P) and intraductal carcinoma of the prostate (IDC-P) are subtypes of

prostate cancer whose clinical significance and relationship has not been unequivocally established so far, with an ongoing debate regarding their prognostic implications.

Even though they share some morphological similarities, DC-P and IDC-P are considered two separate entities [1].

DC-P is a rare subtype of prostate carcinoma, with an incidence < 1% in the pure form. Since 1995, an increase in the incidence of DC-P of 6.78% per year was observed. DC-P has a more aggressive natural history than acinar adenocarcinoma and is more likely to be high-grade, locally-advanced or metastatic at diagnosis. Furthermore, it has been shown that even in localized stages DC-P is associated with higher mortality risk than acinar adenocarcinoma. Also, DC-P usually presents with lower PSA levels, which might influence the detection rate of this disease, but also the identification of tumor progression after treatment [2].

IDC-P is a much debated entity. Although some recent studies suggest that IDC-P represents the intraductal spread of invasive prostate cancer or an aggressive phenotype of prostate cancer [3], others argue that IDC-P might be a precursor lesion of prostate carcinoma [1]. What is well established so far is that IDC-P is associated with high-grade, large volume tumors, with extracapsular extension and it has been shown to be a predictor for early biochemical relapse after treatment [4]. Also, IDC-P seems to be more frequent in patients with familial prostate cancer and BRCA2 carriers and is connected with poorer outcome in comparison with patients without the mutation, even when the stage and grade of cancer at diagnosis are similar [5].

Whether the increase in the incidence of DC-P is real, or it is secondary to improved screening methods and the reporting of IDC-P is included or not in routine pathology reporting remain to be further clarified.

We reviewed 241 patients with localized and locally-advanced prostate cancer, that underwent robotic radical prostatectomy in our department between 2009-2015. We observed that our results were consistent with those already published in the literature regarding the correlation between DC-P or IDC-P and a more advanced stage ($p=0.003$), Gleason score ($p=0.01$) and primary Gleason grade ($p=0.0001$). Furthermore, we observed that, even for cases with localized prostate cancer, there was a statistically significant association between the presence of ductal component (either DC-P or IDC-P) and the biochemical recurrence at 6 and 12 months after surgery ($p=0.016$

and 0.03, respectively).

In conclusion, we observed that the presence of ductal component is related with a worse prognosis even in patients with localized prostate cancer. In this regard, we suggest that the follow-up for these patients should be further personalized.

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Delayed severe thrombocytopenia due to Ipilimumab

Dear Editor,

A 64-year-old female patient had been diagnosed with malignant melanoma by excisional biopsy taken from an irregular mass of the right buccal mucosa. Metastases were identified in the lung and bilateral iliac lymph nodes by PET-CT. B-RAF mutation was positive in the genetic analysis. She received vemurafenib, a tyrosine kinase inhibitor which is specific to BRAFV600 mutation, for 8 months. Due to disease progression she was administered 4 cycles of ipilimumab which inhibits cytotoxic T-lymphocyte antigen-4 (CTLA-4). The patient admitted to the emer-

gency service with oral mucosal bleeding and epistaxis 2 months after the last cycle of ipilimumab. On physical examination, there were no pathologic findings except for petechial and gingival bleeding on the palatine part of oral mucosa. Lab studies revealed the following: Hb:13.9 g/dl, white blood cells:10.4x10⁹/L, platelets: 2x10⁹/L. There was no fragmentation in red blood cells on peripheral blood smear. Platelet counts were concordant with hemogram. Because of the bleeding, 1 g/kg immunoglobulin was given i.v. for 2 days. On the second day of treatment, she received tapering doses of prednisone with a starting dose of 1 mg/kg day. Platelet counts were 58 x10⁹/L and 128

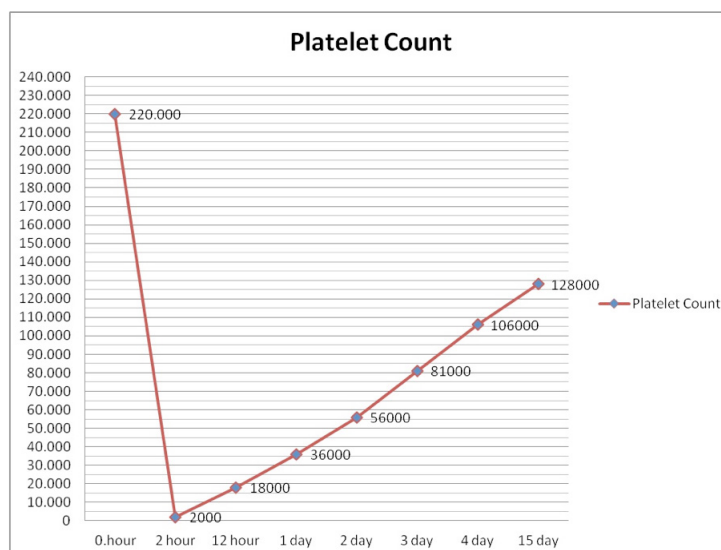


Figure 1. Graphic demonstrating platelet counts day by day.

$\times 10^9/L$ in hemogram on the 3rd and 15th day respectively (Figure 1). Platelet count was increased to $268 \times 10^9/L$ on follow up lab examinations.

Thrombocytopenia can be seen in the clinic with the use of some drugs. Drug-induced thrombocytopenia (DIT) is a relatively common clinical disorder and can be a consequence of decreased platelet production (non immune) or accelerated platelet destruction (immune). Non immune DIT develops due to myelosuppression, a common adverse effect of cytotoxic chemotherapy. Drug induced immune thrombocytopenia (DIIT) is usually a serious clinical disorder characterized by drug-dependent antibodies (DDAbs). Heparin, quinine, penicillin, sulfonamides, non-steroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants are drugs which are most commonly associated with DIIT [1].

Clinically, DIT is a heterogeneous disorder. These patients present with mild to severe thrombocytopenia and spontaneous bleeding, varying from simple ecchymoses, petechiae and mucosal bleeding to life-threatening spontaneous intracranial hemorrhage. Decreased platelet count can be induced by exposure to the drug within 2–3 days if the drug was previously used, or 7 or more days after starting a new drug and delayed thrombocytopenia can be seen in months. The diagnosis is based on the medication history of the patient and lab findings. The differential diagnosis can be made by exclusion of other causes of thrombocytopenia [2,3].

The treatment of DITP is similar to ITP. First, the drug must be discontinued and in 1 or 2 days the recovery of thrombocytopenia begins and usually completes in a week. Intravenous immunoglobulin (IVIG) or 1 mg/kg steroid with IVIG can be given. In the literature there are 2 cases with severe thrombocytopenia which was related to ipilimumab. In one case the platelet count was $3000/mm^3$ and there was no bleeding. Treatment with pulse steroid caused complete platelet recovery within 3 months [4]. In the other case the platelet count was $5000/mm^3$ and there was epistaxis, so first platelet transfusions were carried out, followed by 1 mg/kg prednisolone. Because of the

hemorrhagic bullae in the mouth 1 g/kg/day IVIG was administered and in the 14th day of treatment the platelet count rose to normal levels [5].

As a conclusion, immune mediated thrombocytopenia can occur during or after the treatment with ipilimumab. In our case, there was severe thrombocytopenia which was related with the medicines and developed after 2 months. Therefore, complete blood count monitoring in patients treated with ipilimumab is very important during and after treatment.

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George N. Papanicolaou (1883-1962): studying his first published article in *Science* 100 years on

Dear Editor,

One hundred (100) years have passed since the first publication in *Science* of Dr George Nicholas Papanicolaou (Dr Pap) (Figure 1), who was born in the Aegean coast of Kyme on the island of Euboea in Greece on May 13rd, 1883 and became known worldwide for his innovative revolutionary invention of the Pap smear test [1]. His article was entitled 'Sex determination and sex control in guinea-pigs' and was published in *Science* (*Science, Volume 41, Pages 401-404*) in March 1915 [2]. It was based on his



Figure 1. George N. Papanicolaou at the Cornell University Medical College in the USA with his wife and life companion Andromahi Mavrogeni, known as Mary Papanicolaou.

research performed on vaginal smears of female guinea pigs evaluating cytological changes during their menstrual cycle. His research was performed at the Cornell University Medical College in the USA in collaboration with the Professor of Anatomy Charles Stockard (1879-1939), a pioneer in the scientific fields of Embryology and Zoology [3]. At that time, Papanicolaou's findings added valuable data on the basic understanding of endocrinology of the reproductive organs.

Although many changes in basic research, clinical practice and medical education have occurred since then [4], it is very stimulating that the initial postdoctoral work of Papanicolaou, as a continuity of his PhD, involved animal specimens and was not focused on oncology. However, it provided him all the necessary scientific background with adequate knowledge of techniques and exploration strategies for new Lab methodologies. In the subsequent years, Papanicolaou expanded his experiments in human female cytological material and eventually he managed to develop the Pap smear test, a discovery which to date, even after the introduction of HPV vaccination into clinical practice, remains a principal component of the prevention strategy against cancer in women.

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Disulfide subproteome alterations in the platelets of patients with myelodysplastic syndrome

Dear Editor,

Myelodysplastic syndrome (MDS) encompasses a diverse range of oncohematological diseases affecting

hematopoietic stem cells and their hematopoietic microenvironment. MDS patients are divided into several groups according to the WHO classification [1]; prognostically they are stratified into low-risk and high-risk sub-

groups. MDS patients may suffer from bleeding caused not only by a reduced platelet count (thrombocytopenia), but also by qualitative changes in platelet function. Altered platelet function can be caused by qualitative and/or quantitative changes in the platelet proteome or a specific subproteome (e.g. phosphoproteome, glycoproteome, disulfide subproteome, etc.). There is lack of studies investigating platelet dysfunctions in MDS on the protein level, and therefore this area remains poorly understood. The only exception is a proteomic analysis by Fröbel et al. [2] describing changes on the protein level. In recent years, proteomics has demonstrated a potential to reveal pathophysiological mechanisms, and thus to potentially contribute to MDS management. In this preliminary study of ours, we have focused on the investigation of qualitative and/or quantitative changes in the platelet disulfide subproteome, comparing low- and high-risk MDS patient samples.

A total of 16 MDS samples (low-risk N=8, high-risk N=8) have been analyzed. The median age of low-risk patients was 60 years, with 4 females (50%). The median age of sex-matched, high-risk patients was 63 years. Platelets were isolated from whole blood by differential centrifugation, according to Reicheltova et al. [3]. Platelet proteins were separated using 2D diagonal electrophoresis, and the gels were stained by imidazole-zinc reverse staining, with four technical replicates used. Gels were digitized and processed with Progenesis SameSpots software. Significantly different spots ($p < 0.05$) were submitted for protein identification by tandem mass spectrometry coupled to a nano-LC system, as previously described in detail [4].

We found a significant increase (high-risk vs low-risk MDS, $p = 0.033$) in the normalized volume of a spot in which the glycoprotein Ib beta chain was identified. Glycoprotein Ib beta chain is a part of the glycoprotein Ib-V-IX complex, the initial thrombin receptor in the platelet activation process that mediates platelet adhesion to the exposed surface of the damaged vessel. No other statistically significant differences in disulfide composition between low- and high-risk MDS were observed. Our findings support the theory regarding the affected platelet function in MDS as previously presented by Fröbel et al. [2], who described changes in platelet proteins concerned in $\alpha IIb\beta 3$ signaling. Interestingly, Fröbel et al. did not report any significant differences in the expression profiles of platelet receptors, including glycoprotein Ib. This would strongly indicate that the alteration we have observed in this study was caused by qualitative changes in the glycoprotein Ib-V-IX complex. Therefore, the change we observed would probably be related to the hemorrhagic characteristic of

MDS, contributing thus to complications that accompany the disease. We assume that the alterations in glycoprotein Ib in MDS patients were not caused by platelet (pre) activation, because there were no such changes observed between the results of this study and our previous proteomic study of platelet activation [5]. Our preliminary data show the potential of profiling the platelet disulfide subproteome in MDS patients.

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