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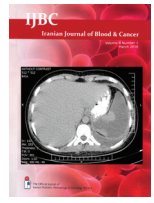

Review Article

Role of Ghrelin in Cancer

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ABSTRACT

Cancer is one of the most fatal diseases in human beings which annually leads to death of 30000 individuals in Iran. Prevention, diagnosis and treatment of cancer is one of the major scientific challenges all around the world. It seems that increased incidence of several cancers such as colon and prostate and their mortality are connected with obesity. It is suggested that obesity and metabolic syndrome are associated with endocrine related cancers and ghrelin pathway may play a role in cancer progression. Ghrelin is a potent regulator of the growth hormone (GH)/ insulin-like growth factor-1 (IGF-1) axis, which is frequently implicated in the development of several neoplasms, including colon cancer. It has been reported that changed ghrelin level as a main regulator of energy homeostasis plays an important role in carcinogenesis. Also, antiproliferative effects of ghrelin in lung and breast carcinoma cell lines have been detected in some studies . In this paper, ghrelin and its role and function in cancer is discussed.

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Introduction

One of the most fatal diseases in human beings is cancer which annually leads to the death of about 30000 persons in Iran.[1] This incurable disease continues to be a major problem in recent years.[1-3] It seems that increased risk of the expansion of several cancers such as colon and prostate cancers, and their risk with mortality are connected to obesity.[4] Hormonal abnormalities in obese people such as low ghrelin level may play a key role in cancer development. Moreover, the undesirable side effects of currently standard therapies for colon and androgen independent prostate cancers lead to persistent need for new and more powerful therapeutic options.[4]

Ghrelin

Ghrelin is a 28-amino acid peptide[5-7] mainly produced in the stomach[8] of humans and rodents.[3] It is also produced by a wide variety of tissues and acts as a paracrine/ autocrine factor.[8] About 60–70% of circulating ghrelin is originated by stomach, while about up to 30% is produced in the small intestine.[9] Moreover, other tissues including pancreas and cardiovascular system could produce ghrelin.[10] Albeit ghrelin expressed in heart is lower than that in the stomach, but it exerts a cardioprotective effect via unknown mechanisms.[11] Ghrelin known as a brain-gut peptide can induce changes such as increased food intake and body fat through altered appetite and amount of food intake.[12,13]

Ghrelin plays a significant role in release of GH and triggers secretion of hepatic IGF-1. Both GH and IGF-1 as anabolic hormones can increase lean body mass via stimulating skeletal muscle growth and inhibiting skeletal muscle protein breakdown.[14] It has been reported that ghrelin causes positive energy balance via decreasing fat utilization by GH-independent mechanisms.[15] Moreover, the secretion of ghrelin is stimulated via energy restriction and acetylcholine and reduced via gastrectomy, food intake, glucose, insulin and somatostatin releasing

inhibitory factor (SRIF).[10] Also it plays an important role in metabolic response to starvation via modulating insulin secretion, glucose metabolism and amino acid uptake.[3] Ghrelin stimulates the differentiation of preadipocytes and inhibit lipolysis. Therefore it has a main role in the process of adipogenesis.[16] It increases anxiety-like behavior and memory retention in rodents and may promote sleep in human beings.[16] Inhibition of insulin secretion and regulation of gluconeogenesis/glycogenolysis was accomplished in the presence of ghrelin; therefore, it regulates glucose homeostasis in many aspects.[17] Ghrelin is pertained to G protein-coupled receptor family.[18,19] Ghrelin could cause weight gain through growth hormone secretion and as a result increasing food intake and reducing fat utilization in rodents.[20] It also moderates some actions of gastrointestinal tract and alters the growth processes of neoplastic tissues.[2]

Ghrelin exists in two molecular forms: acylated or octanoylated and unacylated or desoctanoylated.[2] Unacylated ghrelin via ghrelin O-acyltransferase (GOAT) enzyme can be acylated[8] and yields the natural ligand of the only known ghrelin receptor.[8] Figures 1 and 2 show unacylated and acylated ghrelin, respectively.

Endocrine activity of ghrelin is dependent on its acylation mediated by GH secretagogue (GHS) receptor and des-acyl ghrelin has no endocrine activity and does not bind to GHSR-1a; however, its mechanism of action is not defined well.[11]

Ghrelin and Cancer

Gastrointestinal cancers, especially colorectal cancers are associated with obesity and strong relationship is observed between these cancers and environmental factors in addition to genetic factors. Obesity is associated with hyperisulinemia or insulin resistance with elevated leptin and decreased ghrelin serum levels. Obesity and metabolic syndrome are associated with endocrine related cancers and ghrelin has proposed to have some influencial role in cancer development or progression.[21] Ghrelin is a potent regulator of the GH/IGF-I axis which is frequently implicated in the development of several neoplasms, including colon cancer.[2] It has been observed that circulating changes in leptin and ghrelin levels as two main regulators of energy homeostasis could play important role in carcinogenesis.[2] Clear-cut data about

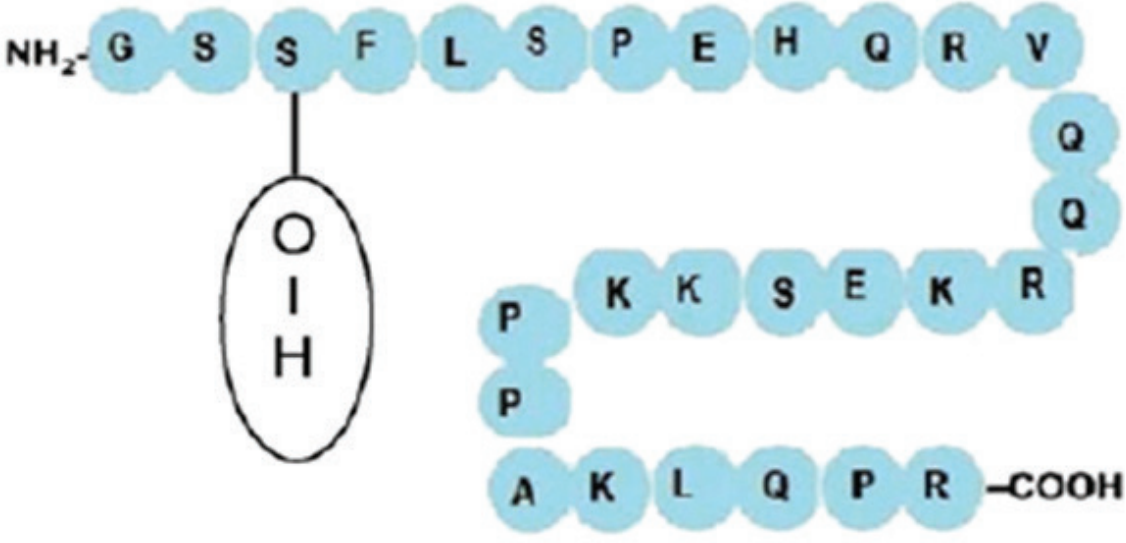

Figure 1: Unacylated ghrelin[9]

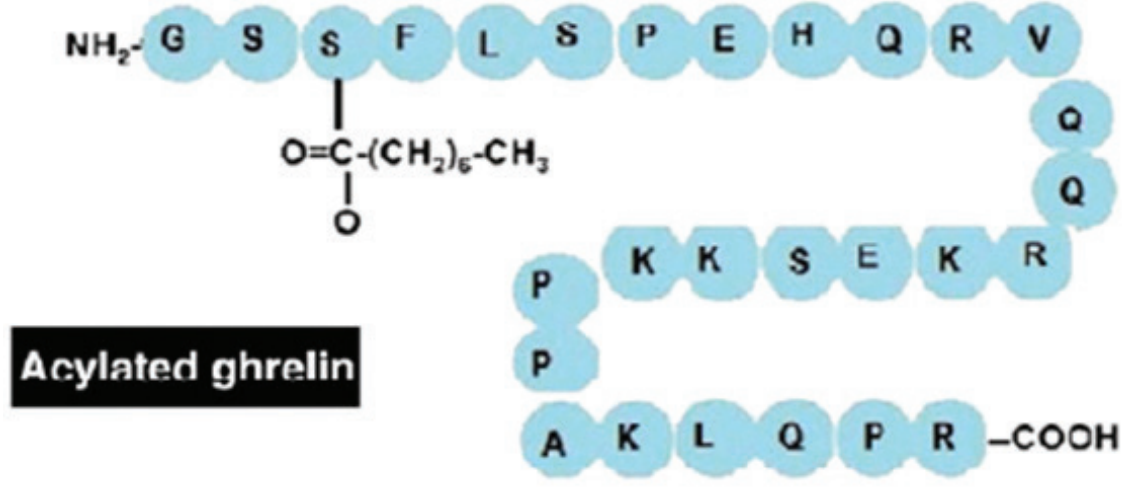

Figure 2: Acylated ghrelin[9]

ghrelin and its effects on proliferative pathologies is contradictory for now.[3]

Ghrelin and its receptors exist in many endocrine and non-endocrine tumor cell types such as gastroenteropancreatic, pituitary, prostate, breast and other related cancer cell lines.[8] Ghrelin controls neoplastic cell proliferation, but precise role of ghrelin still is not clear.[8] Some studies have reported that ghrelin has proliferative properties in cancers. Study in canine mammary carcinoma showed that there are high levels of ghrelin and GHS-R in metastatic tumors.[17]

Ghrelin has shown antiproliferative effects in lung and breast carcinoma cell line and proliferative effects in prostate, pancreatic and adrenal cancer cell lines.[3] Another study reported that ghrelin may inhibit growth of breast, thyroid and lung cancer cell lines independent of the GH releasing effect. In contrast, ghrelin may induce a proliferative response in some other cell lines via IGF-1 and GH with tumorigenic potential.[16]

The effect of ghrelin on breast cancer cell proliferation is discovered by Jeffery et al. in their study.[22] They evaluated proliferation of breast cancer cell lines MDAMB-231 and MDA-MB-435 and observed that growth rate of MDA-MB-231 cells was significantly increased in the presence of ghrelin.[9]

Volante et al. in another study reported that high concentrations of ghrelin (100 nmol/ l–1 µmol/l) has anti-proliferative actions in thyroid cancer cells. They also suggested that autocrine circuits of ghrelin may be operating in the growth control of thyroid follicular tumors.[23]

De Vriese et al. evaluated the autocrine proliferative effect of ghrelin on human leukemic HL-60 and THP-1 cell lines.[24] The human leukemic cell lines did not express the functional GHS-R1a, but expressed GHSR1b. They observed that addition of octanoylated or des-acyl ghrelin did not exert any effect on leukemic cell proliferation. Another study has shown that ghrelin levels in gastric cancer tissues were significantly lower than normal tissues and a significant difference was observed according to the degree of cell differentiation.[9]

Researchers also examined the proliferative effect of ghrelin and its mechanisms of action on pituitary cell line (GH3). They showed that ghrelin, at 10−10 to 10−6 M concentrations exerts GH3 pituitary somatotroph cell proliferation. In addition, activation of the MAPK pathway and inhibitors of the extracellular signal-regulated kinase 1 and 2 (ERK 1/2), protein kinase C (PKC) and tyrosine phosphatase pathways were evaluated. The results showed that PKC-MAPK-dependent and tyrosine kinase-dependent pathways are mediators of proliferation of GH3 cells in the presence of ghrelin.[9]

Other studies have indicated expression of ghrelin in leydig cell tumors and dysgenetic sertoli cells. They described that differentiated leydig cell tumors were associated with ghrelin expression;[25] Whereas, poorly differentiated types were negative for ghrelin expression.[9] Karapanagiotou et al. evaluated the role of ghrelin in advanced non-small cell lung cancer patients and observed significantly higher ghrelin serum levels in these patients.[26]

A starting role of ghrelin in cancer cell migration and invasion has also been detected. Ghrelin concentrations of 100 nM could cause increment of migration ability of canine carcinoma cell lines.[18]

Conclusion

The existing knowledge regarding ghrelin and its effect on proliferation processes is contradictory. However, ghrelin abnormalities in obese population may have contribution in tissue growth and cancer development.

Conflict of Interest: None declared.

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In Vitro Evaluation of the Anti-bacterial Effect of Human Platelet Concentrate

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ABSTRACT

Background: Recently the role of platelets in the tissue regeneration, wound healing and prevention and control of infections has been reported. We aimed to assess the antimicrobial effect of human platelet concentrate against six bacteria, commonly found in wound and hospital-acquired infections.
Methods: In vitro susceptibility to samples of 10 random human platelet concentrates was determined by disc diffusion method against Staphylococcus epidermidis, Staphylococcus aureus, Micrococcus luteus, Escherichia coli, Pseudomonas aeruginosa, and Proteus vulgaris. The assay was performed in triplicate for each strain and the antibacterial activities were assessed by measuring the zones of inhibition at 20, 24 and 48 hours after incubation at 37 °C.
Results: Human platelet concentrate showed antibacterial activity against Staphylococcus aureus and Staphylococcus epidermidis with the mean diameter zone of inhibition of 11.4±1.1 and 10.2±1.1 mm, respectively. Whereas, no activity was observed against Micrococcus luteus, Pseudomonas aeruginosa, Escherichia coli, and Proteus vulgaris. Also, there was no significant difference in antibacterial effect of human platelet concentrate after 20, 24, and 48 hours.
Conclusion: Human platelet concentrate which is a biocompatible and safe product could be potentially useful in wound healing and hospital-acquired infections.

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Introduction

Platelets are mainly known for their crucial role in the hemostasis.[1] Various recent studies have also indicated the important role of platelets in tissue regeneration, wound healing, and prevention and control of infection.[2-7] Therefore, nowadays platelet products are used in various fields of medicine, including dermatology, cosmetic and plastic surgery, ophthalmology, orthopedics, rheumatology, sports medicine and dentistry. Undoubtedly, such a widespread use of platelet products is largely related to the anti-inflammatory properties of platelets and the presence of multiple growth factors in these natural products along with their potential antibacterial activity.[1,8,9]

Bacterial infections are among the most serious complications that provoke many social health concerns. Although the use of antibiotics is recommended for certain infectious situations, they can cause various adverse reactions. Improper usage of antibiotics may contribute to the increasing emergence of antibiotic resistance which has been referred to as one of the world's most pressing health problems.[10]

Considering the need for new effective, biocompatible and safe antimicrobial compounds, and since the antibacterial effect of platelet concentrate (PC) against some bacteria has been reported in a few in vitro

studies,[2,8,11-14] we aimed to investigate the antibacterial effect of PC against three gram negative and three gram-positive bacteria which are mainly responsible for wound and hospital-acquired infections.

Methods

Bacteria and Preparation of Inoculums

Three gram-negative bacteria including Escherichia coli (PTCC 1399), Pseudomonas aeruginosa (PTCC 1430), and Proteus vulgaris (PTCC 1079) and three gram-positive bacteria including Staphylococcus epidermidis (PTCC 1435), Staphylococcus aureus (PTCC 1431) and Micrococcus luteus (PTCC 1408) were selected for the study. The bacterial strains were obtained from Pasteur Institute (Tehran, Iran) and maintained on Nutrient agar at 4 °C at Islamic Azad University laboratory. To prepare inoculums of bacteria culture, the stock culture from Nutrient agar was subcultured on Muller-Hinton agar (Merck, Germany) and incubated overnight at 37 °C, then a suspension of freshly grown bacteria in sterile distilled water was prepared for each strain with an optical density equal to 0.5 McFarland (1×10^8 CFU/mL).

Platelet Concentrate Preparation

Each of 10 random PCs was obtained from Tehran Blood Transfusion Center on the day of experiment. It should be noted that PCs prepared from whole blood of healthy blood donors using platelet-rich plasma method[15] were stored and shipped at 20 to 24ºC along with continuous agitation during storage.

Determination of Antibacterial Activity

In vitro laboratory susceptibility to PC was determined by disc diffusion method[16] on Mueller–Hinton agar (MHA). For this purpose, agar plates were coated with one of the following bacterial strains: Staphylococcus epidermidis, Staphylococcus aureus and Micrococcus luteus as Gram-positive bacteria and Escherichia coli, Pseudomonas aeruginosa and Proteus vulgaris as Gram-negative bacteria. Then standard 6 mm discs soaked with PC and positive or negative control were placed on the coated agar media. The inoculated agar plates were then incubated at 37 °C for 48 hours. The baseline antimicrobial activity was assessed by measuring the diameter zones of inhibition after 20, 24, and 48 hours after incubation at 37 °C and results were expressed as mean ± SD. It should be noted that the assay was performed in triplicate for each strain and Penicillin and Gentamicin were used in all assays as positive controls for Gram-positive and Gram-negative bacteria, respectively. Mueller-Hinton Broth was used as a negative control.

Results

The mean values for zone of inhibition produced by PC, positive control and negative control against six bacteria are shown in table 1. PCs showed antibacterial activity against Staphylococcus aureus (figure 1) and Staphylococcus epidermidis (figure 2) with the mean diameter zone of inhibition of 11.4±1.1 and 10.2±1.1 mm, respectively. There was no activity against Micrococcus luteus, Pseudomonas aeruginosa, Escherichia coli and Proteus vulgaris. Moreover, there was no significant difference in antibacterial effect of PCs after 20, 24, and

Table 1: Zones of inhibition, exerted by platelet concentrate, positive control and negative control against six bacteria after 24 hours of incubation

Sample \ Bacteria	Staphylococcus epidermidis	Staphylococcus aureus	Micrococcus luteus	Escherichia coli	Pseudomonas aeruginosa	Proteus vulgaris
Platelet Concentrate	10.2±1.1 mm	11.4±1.1 mm	-	-	-	-
Positive control	19±2.0 mm	40.9±1.8 mm	59±3.7 mm	21±2.1 mm	19.5±0.7 mm	19.6±0.7 mm
Negative control	-	-	-	-	-	-

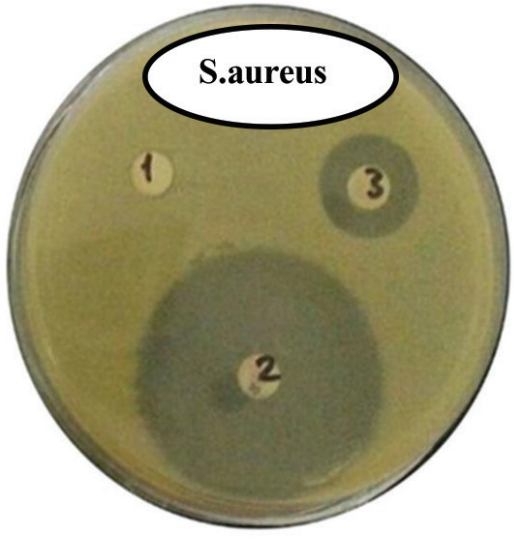

Figure 1: The zone of inhibition exerted by 1-Mueller Hinton Broth (negative control), 2-Penicillin (positive control) and 3-Platelet concentrate against Staphylococcus aureus after 24 hours of incubation

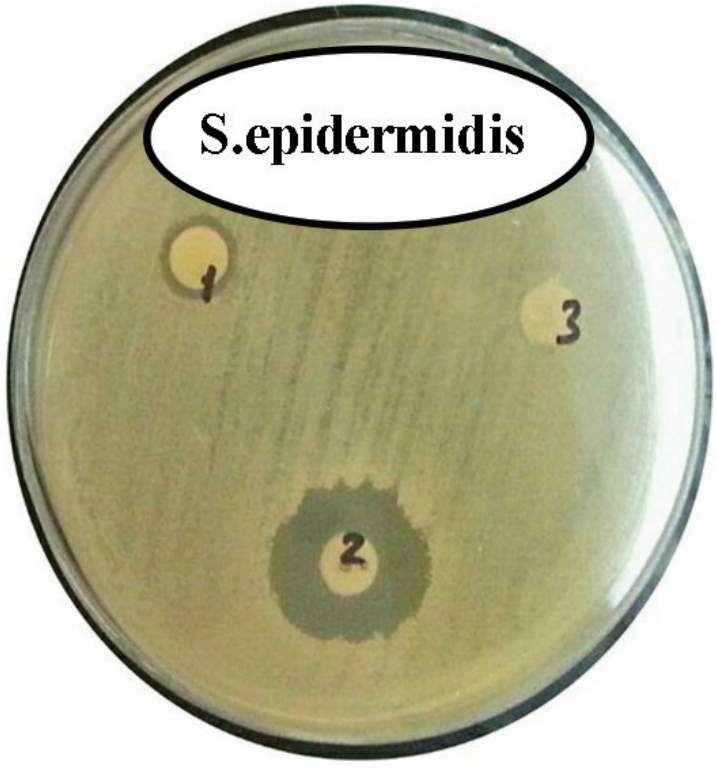

Figure 2: The zone of inhibition exerted by 1- Platelet concentrate, 2-Penicillin (positive control) and 3-Muller Hinton Broth (negative control) against Staphylococcus epidermidis after 24 hours of incubation.

48 hours.

Discussion

Despite a wide spectrum of available potent antimicrobials, bacterial infection remains a major problem. This is largely due to the emergence of bacterial resistance, caused by the inappropriate or inadequate use of antibiotics.[10] Therefore research for finding an alternative treatment and a solution for antibiotic resistance is crucial.

In the case of wound infections and hospital-acquired infections, it seems that platelet products could be appropriate adjuncts to antibiotics. Platelets can interact with microbial pathogens directly and indirectly through multiple molecular and cellular mechanisms. It has been suggested that platelets not only reduce incidence of bacterial infections but also promote wound healing.[1,5,6] Therefore, platelet products have recently attracted interest in this regard. But it seems that research in this field is still limited and insufficient. This study was designed to determine the in vitro antibacterial activity of human platelet concentrates against 6 common causes of wound and hospital-acquired bacterial infections.

The results of this study confirmed the previously reported antibacterial effects of human platelet concentrates against S. aureus.[4,8,11,13,14,17] The observed antibacterial activities of PCs against S. epidermis were similar to findings of Anitua et al., while Burnouf et al. found different results in their research.[3,8] On the other hand, PCs were not effective against four other bacteria in our study. It should be noted that previous studies conducted on P. aeruginosa and E.coli yielded contradictory results.[3,9,11] PCs have not been tested against M. luteus and P. vulgaris yet.

It seems that donor's variability along with differences in the quality, viability, activation and degradation rate of platelets could cause variation in the susceptibility pattern of the gram-positive and gram-negative bacteria in comparison to other studies. Our study used PTCC bacterial strains which may behave in a way different from clinical isolates or ATCC bacterial strains. Therefore, further studies (both in-vitro and in-vivo) are needed to investigate the antimicrobial effect of platelet concentrates against viruses, fungi and other bacterial strains along with similar studies using clinical isolates.

Conclusion

The findings of this study regarding the antibacterial effect of PCs against S. aureus and S. epidermidis were consistent with some other studies supporting the clinical use of platelets as a biocompatible and safe product in wound healing and hospital-acquired infections. Further research on PCs should be employed to determine exact antibacterial spectrum, their antimicrobial capacity along with antibiotics and their efficacy in in-vivo conditions.

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Evaluation of Thyroid Dysfunction during Imatinib Therapy in Chronic Myeloid Leukemia

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ABSTRACT

Background: Imatinib mesylate is the first generation of Tyrosine kinase inhibitors (TKI) and highly effective in the treatment of chronic myeloid leukemia (CML). We aimed to evaluate thyroid function at baseline and at 1, 3, 6 and 12 months after initiation of Imatinib mesylate therapy in 20 newly diagnosed BCR-ABL positive CML patients.
Methods: This study was done during 2013-2014, 20 new cases with Philadelphia chromosome-positive CML without any underlying thyroid disorder or drug history interfering with Imatinib mesylate were enrolled. Thyroid function tests including serum Thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) were assessed at baseline and during follow-up.
Results: Mean age at diagnosis was 60.4 years. 14 (70%) patients were male. Mean value for TSH, FT4, FT3, Anti-TPO, and Anti-Tg before treatment were 2.82 mIU/L, 1.39 ng/dl, 325.50 ng/dl, 30.35 IU/ml and 39.40 IU/ml, respectively. The mean value for TSH, FT4, FT3 and Anti-TPO 1, 3, 6, and 12 months after initiation of Imatinib mesylate were not statistically significant.
Conclusion: Based on the results of the study, there was no significant change in thyroid function tests during treatment with Imatinib mesylate and all laboratory variables were in normal ranges.

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Introduction

Chronic myeloid leukemia (CML) accounts for about 30% of all leukemias. It *occurs in all age* groups, 20% of patients are younger than 25 years.[1] Tyrosine kinase inhibitors (TKIs) block tyrosine kinase signaling pathways that modulate oncogenesis.[2] They exhibit vascular and antiangiogenic properties by interacting with VEGF.[2] TK proteins are a broad group of cell membrane proteins (about 500 different proteins) involved in important cellular activities such as proliferation, differentiation, and apoptosis. TKIs are new and small designed targeted molecules that are analog to ATP molecule structure and arrive to compete with real ATP for binding to tyrosine part of TK molecule. Thus, they preclude TK phosphorylation via an inhibitory competitive replacement and cutting-off TK-dependent oncogenic pathways.[3-5] The increased demand for levothyroxine induced by imatinib in patients who are receiving levothyroxine replacement therapy might indicate increased peripheral metabolism of thyroid hormones.[6] Thyroid dysfunction is a known side effect of some tyrosine kinase inhibitors such as sunitinib and sorafenib[7] while imatinib has been shown to induce hypothyroidism and increased requirement for levothyroxine in thyroidectomized patients.[6,8] There are

few retrospective studies on CML patients treated with imatinib which have demonstrated conflicting effects on thyroid function tests.[9] We have prospectively studied thyroid function tests at baseline and at 1, 3, 6 and 12 months after initiation of treatment with imatinib in 20 newly diagnosed BCR-ABL positive patients with CML.

Materials and Methods

This study was approved by Birjand University Ethics Committee, Birjand, Iran. In this study from February 2013 to August 2014, 20 new cases with Philadelphia chromosome-positive CML without any underlying thyroid disorder or any history of using drugs interfering with imatinib or having effect on thyroid function (Dexamethasone, Phenytoin, Carbamazepine, Rifampin and Phenobarbital) were enrolled. Thyroid function tests at baseline and during follow-up included serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg). Serum TSH, FT3, and FT4 were measured by an electrochemiluminescence immunoassay (ECLIA; Roche, Grenzach-Wyhlen, Germany); Anti-TPO and Anti-Tg by a luminescence immunoassay with time-resolved amplified cryptate emission technology (Brahms, Hennigsdorf, Germany) before and 1, 3, 6 and 12 months after initiation of imatinib therapy (400 mg per day). Serum samples were collected, handled, and analyzed according to internal standard operating procedures. Laboratory reference ranges were 0.27–4.20 mIU/L for TSH, 260-501 ng/dl for FT3, and 0.9–1.9 ng/dl for FT4. Upper limits for antibody positivity were >60 IU/ml for Anti-Tg and Anti-TPO.[9]

Results

The patients' mean age at diagnosis was 60.4 years. 14 (70%) patients were male and 6 (30%) were female. The mean values for TSH, FT4, FT3, Anti-TPO, and Anti-Tg before treatment were 2.82 mIU/L, 1.39 ng/dl, 325.50 ng/dl, 30.35IU/ml, and 39.40 IU/ml, respectively (table 1). Mean values for TSH, FT4, FT3 and Anti-TPO 1, 3, 6 and 12 months after initiation of Imatinib were not statistically significant. There was a significant difference in mean values of Anti-Tg 1, 3, 6 and 12 months after initiation of treatment with imatinib (P=0.014, 0.008, 0.003 and 0.002, respectively).

Discussion

CML is the most common myeloproliferative disorder in adults with a characteristic cytogenetic abnormality known as t(9:22).[10] De Groot et al.[6] reported the results of a study on 11 patients who had received imatinib (1 with gastrointestinal stromal tumor and 10 with *medullary thyroid carcinoma (MTC)*; eight of these patients had previously undergone thyroidectomy and were on thyroid hormone replacement therapy. Increased thyroid hormone requirements were observed while on imatinib therapy. In another study by de Groot et al.[8] nine out of 15 advanced MTC patients who were treated with imatinib, had previously undergone total thyroidectomy and were on thyroid hormone replacement therapy, all them had increased thyroid hormone requirements while on therapy. On the other hand, patients with intact thyroid glands remained euthyroid while on imatinib. Therefore, both studies showed that all patients with intact thyroid glands receiving imatinib had no thyroid dysfunction. In a study from Desai et al.[11] on 42 patients treated with sunitinib for a median of 37 weeks (range, 10 to 167), 4 patients (10%) developed isolated TSH suppression and 7 patients (17%) experienced transient, mild TSH elevations. The risk for hypothyroidism increased with the duration of treatment with sunitinib. Six (40%) of 15 hypothyroid patients had suppressed TSH concentrations before developing hypothyroidism suggesting thyroiditis. Kim et al.[9] retrospectively reviewed thyroid function tests in 10 patients who were treated with dasatinib, 2 patients were on levothyroxine prior to starting therapy, 5 patients developed hypothyroidism (4 subclinical, 1 clinical), and two patients had subclinical hyperthyroidism, none of which required treatment. Dora et al.[12] found no adverse effect of imatinib on thyroid function and lack of correlation between TSH levels with dose, duration, or even cumulative dose of imatinib therapy suggests that this drug has no side effect on thyroid function.

The mechanism of imatinib-induced subclinical or clinical hypothyroidism was stimulation of T3 and T4 clearance owing to elevated activity of liver microsomal enzyme, uridine-diphosphate-glucuronyltransferase (UGTs), which needed to be stabilized.[13] Sorafenib has been associated with hypothyroidism in patients with previously normal thyroid function, with an incidence of 18% in one study[14] and 67% in another study.[15] Other TKIs have also been associated with thyroid disease in patients with previously intact thyroid function.[9] In a retrospective study of 64 patients treated for CML, hypothyroidism was seen in 13%, 50%, and 22% of patients treated with imatinib, dasatinib, or nilotinib, respectively.[9] The incidence of preceding transient thyrotoxicosis was also high suggesting a phase of thyroiditis preceding the

Table 1: Thyroid tests in patients with chronic myeloid leukemia before and after Imatinib therapy

Thyroid tests	Before treatment with imatinib	1 month after treatment	3 months after treatment	6 months after treatment	12 months after treatment
FT3, ng/dl	325.5	333.5	333	321	312
FT4, ng/dl	1.39	1.36	1.22	1.33	1.34
TSH, mIU/l	2.82	2.67	2.88	2.94	3.02
Anti-TPO, IU/ml	30.35	29.45	32.7	33.05	33.15
Anti-Tg, IU/ml	39.4	50.75*	55.85*	60.3*	56.3*

*P value<0.05 was significant; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; Anti-TPO, anti-thyroid peroxidase; Anti-Tg, anti-thyroglobulin

loss of function.[9] The main mechanism of TKI-induced hypothyroidism is unclear. Rare cases of thyrotoxicosis preceding the development of hypothyroidism suggest that there is a preceding thyroiditis. Some suggestions for the mechanism of hypothyroidism associated with TKIs include direct toxic effects on thyrocytes, reduced TPO activity,[16] impaired iodine uptake,[17] or stimulation of Hashimoto thyroiditis;[18] although Hashimoto thyroiditis is improbable to be the main mechanism because of the low prevalence of Anti-TPO antibodies in patients with sunitinib-induced hypothyroidism.[17,19] The most likely explanation is that the thyroid dysfunction is related to the effects of these factors on tyrosine kinases involved in vascular function such as VEGFR. This could cause attenuation of the thyroid blood flow to this extremely vascular gland. If the blood flow decreases rapidly, an ischemic thyroiditis could result leading to a transient period of thyrotoxicosis. If the decreased blood flow develops more slowly, gradual thyroid destruction may occur with resulting hypothyroidism.[14] Supporting evidence for this theory includes the finding that thyroid cells express VEGF and VEGFR mRNA and studies on mice have shown glandular capillary regression with TKI exposure.[20] Two recent case reports demonstrated reduced thyroid volume and vascularity by doppler ultrasound,[17,21,22] with rapid increase in size of the thyroid following cessation of sunitinib. The reduced thyroid volume (because of reduced blood flow) may also explain the impaired radioactive iodine uptake in vivo[17] but not in vitro.[23]

Conclusion

Based on results of this study, there was no significant change on thyroid function tests during imatinib therapy and all variables were within normal ranges. However, larger studies with larger sample size are recommended to prove imatinib-induced hypothyroidism.

Conflict of Interest: None declared.

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ORIGINAL ARTICLE

Evaluation of the Seroprevalence of Transfusion Transmissible Infections among Blood Donors in a Tertiary Care Hospital of North India

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ABSTRACT

Background: Unsafe transfusion practices put patients at high risk of transfusion transmissible infections. We aimed to evaluate the prevalence of transfusion transmissible infections (including Human Immunodeficiency Virus [HIV] 1 and 2, Hepatitis B Virus [HBV], Hepatitis C Virus (HCV) and syphilis) during a period of 18 months among blood donors in the Blood Bank of Lady Hardinge Medical College.

Methods: The prevalence of markers of HIV, HBV, HCV and syphilis was evaluated among blood donors from January 2013 to June 2014. All donors who came to donate blood in the blood bank as well as voluntary donors who donated in the outreach blood donation camps were included in the study.

Results: 15713 donations were received. The overall seroprevalance of HIV, HBV, HCV and syphilis was 0.2%, 1.54%, 0.49%, and 1.45%, respectively. The seroprevalence of HBV, HCV and syphilis was 0.57%, 0.14%, and 0.53%, respectively amongst voluntary donors.

Conclusion: transfusion transmissible infections were less common among voluntary donors than those among replacement donors. Awareness of the general population about voluntary blood donation should be created to minimize the chances of spreading transfusion transmitted infections.

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Introduction

Unsafe transfusion practices put patients at high risk of transfusion transmissible infections. Proper donor counseling and selection along with sensitive screening tests ensure elimination or at least reduction of the risk of acquiring transfusion transmissible infections.[1] Efforts are being made to provide almost zero risk transfusion.

We aimed to evaluate the prevalence of transfusion transmissible infections (including Human Immunodeficiency Virus [HIV] 1 and 2, Hepatitis B Virus [HBV], Hepatitis C Virus [HCV] and syphilis) during a period of 18 months among blood donors in Blood Bank, Lady Hardinge Medical College.

Materials and Methods

The prevalence of markers of HIV, HBV, HCV and syphilis was evaluated among blood donors from January 2013 to June 2014. All donors were subjected to pre-transfusion counseling and screening which was done by qualified, trained doctors and staff. Strict criteria were used for donor selection. Donors who did not fulfill the criteria for blood donation, paid and commercial donors and those with history of high risk behavior were deferred. Consent for infectious marker testing was obtained from all the donors at the time of pre-test counseling prior to blood donation. All donors who came to donate blood in the blood bank as well as voluntary donors who donated in the outreach blood donation camps were included in the study.

All donor blood samples were collected at the time of blood donation from the primary bag and were screened for transfusion transmissible infections. HIV, HBsAg,

HCV testing was done by ELISA using BIORAD GENSCREEN ULTRA HIV Ag-Ab kit (4th generation ELISA), BIORAD Monolisa HBsAg ULTRA kit (3rd generation ELISA) and BIORAD HCV Ag-Ab ULTRA kit (4th generation ELISA) respectively. The BIORAD TPHA 500 test kit was done for syphilis. All seropositive cases were repeated in duplicate before being labeled as seropositive.

The procedures followed in the study were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki declaration of 1975, as revised in 2000.

Results

A total of 15713 donations were received. The overall seroprevalance of HIV, HBV, HCV and syphilis was 0.2%, 1.54%, 0.49% and 1.45% respectively. Prevalence of HBV was the highest among the various markers.

Out of the total donations, 13618 (86.67%) were replacement donors and the rest (13.33%) were voluntary donors. Prevalence of all the transfusion transmissible infections was more common in the replacement donors as compared to voluntary donors (table 1).

None of the voluntary donors tested positive for HIV. The seroprevalence of HBV, HCV and syphilis was 0.57%, 0.14% and 0.53% respectively amongst voluntary donors. Prevalence for HBV was the highest in this group also.

When the age wise distribution of transfusion transmissible infections was evaluated, HIV was found be most prevalent in donors aged 30-39 years, while both HBsAg and HCV positivity was most prevalent in the 20-29 year-old age group (table 2A).

Most donors were male (96.77%). All the transfusion transmissible infections were more common in men compared with women (table 2B). None of the HIV positive donors were female and 0.2% of the total male donor population tested positive for HIV. In addition, seropositivity for HBsAg, HCV and TPHA was higher in the male donors compared with the female donors (table 2B).

Discussion

According to estimations in 2012, there were 20.89 lakh HIV infected people in India.[2] The national average for HBV and HCV positivity in healthy donor population is around 4.7%[3] and 1-1.5%[4] respectively.

Blood donors from the community or the replacement donors in hospitals do not fall in the high risk group like intravenous drug users, professional health donors, or sex workers. So, prevalence of HBV, HIV and HCV among healthy blood donors or replacement doors reflects the disease prevalence in the general community. Also, it estimates the risk of chance of acquisition of these infections during blood transfusion.[5]

Table 3 sums up the results of seroprevalence of Transfusion transmissible infections from various regions of our country. The difference in the prevalence rates of the different studies is due to the difference in the population under study, the education and awareness level of the population, the type of donors and the levels to which individuals with risk factors for blood borne viral infections that have been excluded. Also, the difference in seropositivity of different markers in various series can be explained by the differences in the method used for testing and criteria of positivity. Seropositivity reflects the social, cultural, religious and sexual practices. Evaluation of transfusion transmissible infection among blood donors allows assessment of the prevalence of infections

Table 1: Comparison of TTIs in replacement and voluntary donors

	HIV	HBV	HCV	Syphilis
Replacement donors	31	230	74	216
Voluntary donors	0	12	3	11
Total	31	242	77	227

Table 2A: Age wise prevalence of TTIs

Age group (years)	HIV	HBV	HCV	Syphilis
18-19	0	12	2	1
20-29	11	105	40	80
30-39	15	96	26	97
40-49	4	25	8	40
50-59	1	4	1	9
60-65	0	0	0	0
Total	31	242	77	227

Table 2B: Gender wise prevalence of TTIs

Gender	HIV	HBV	HCV	Syphilis
Male	31/15216 (0.2%)	239/15216 (1.57%)	76/15216 (0.5%)	224/15216 (1.47%)
Female	0/497 (0%)	3/497 (0.6%)	1/497 (0.2%)	3/497 (0.6%)
Total	31/15713	242/15713	77/15713	227/15713

Table 3: Prevalence of TTIs in different studies

Study	HIV	HBV	HCV	Syphilis
Bhawani et al 2004-9 (Andhra Pradesh)[6]	0.39%	1.41%	0.84%	0.08%
Shah et al Jan 2006- July 2013 (Gujarat)[7]	0.16%	0.98%	0.11%	0.23%
Ahmed Z et al 2008-11 (Karnataka)[8]	0.1%	0.5%	0.08%	0.07%
Deshpande et al 2007-11 (Maharashtra)[9]	0.56%	3.75%	0.46%	0.09%
Sethi B et al 2007-11 (Uttrakhand)[10]	0.19%	0.63%	0.2%	0.02%
Lathamani et al Jan 2008-March 2010 (Karnataka)[11]	0.08%	0.53%	0.098%	0.09%

in the blood donor population and therefore the safety of the collected donations and the recipients. It allows estimation of the risk of accidental acquisition of these infections during blood transfusion. Also it gives an idea of the epidemiology of these diseases in the community.

A similar study was done in our institution by Pahuja et al in which the prevalence of HIV, HBV, HCV was 0.56%, 2.23%,0.66% respectively from 2002-2005. Syphilis was not evaluated. All three viral markers were tested using 3rd generation ELISA kits.[12] It is noted that the seroprevalence of all of them has declined in the period Jan 2014 – June 2015.

The risk of transmission of HIV, HBV and HCV has reduced in the recent years because of improved donor selection, increased vigilance and making screening of all donated blood for Transfusion transmissible infections mandatory. Donors having history of being HIV, HBV or HCV positive are permanently deferred.[13] Donors must be screened for high risk behavior related diseases since most of the transfusion transmissible infections exist as asymptomatic diseases in the hosts. In India, the risk of transfusion transmission of HIV, HBV and HCV may be alarming due to high prevalence of anti-HIV-1, anti-HCV and HBsAg (0.5%, 0.4% and 1.4% respectively) in blood donors.[14] Rising trend in the prevalence of syphilis among blood donors reflects the changing lifestyle and social norms.

Higher seropositivity among males than females may be due to the heterosexual promiscuity.

Voluntary donors are motivated blood donors who donate blood at regular intervals. Replacement donors are usually one time donors who donate blood only when a relative or a friend is in need of blood. Transfusion transmissible infections among voluntary donors were less common than those among replacement donors. Awareness of the general population about voluntary blood donation should be created to minimize the chances of spreading transfusion transmitted infections. Replacement donors carry a relatively higher risk of transfusion transmitted infections due to chances of missing professional donors during donor screening procedures as professional donors are aware of the criteria for deferral. Hence, blood from replacement donors should be accepted only in cases of dire emergencies when transfusion of blood would be lifesaving.[7] However, this is often not possible in our country since the number of voluntary donations are too less to cater to the demand of blood.

Efforts should be made to focus on voluntary donation by spreading awareness in the population about the scarcity of blood and sensitizing the general population for the need of blood. Meanwhile, individuals should also be educated regarding the Transfusion transmissible infections which are dangerous to both blood donors and recipients. For this, voluntary blood donation camps have to be arranged and proper counseling of the donors should be done.

Proper donor selection, education and uniform implementation of laboratory screening tests should be the points kept in mind. A more detailed history regarding sexual exposure of blood donors is advocated. Also, a lot more needs to be done regarding employing more field workers (Counselors) for voluntary blood donation. Success of a voluntary blood donation camp depends upon the number of donors. Also, judicious use of blood helps in reducing the transmission of transfusion transmissible infections, as lesser the transfusion, lesser the replacement donation and lesser the Transfusion transmissible infections.

Conclusion

Evaluation of Transfusion transmissible infections among blood donors allows assessment of the prevalence of infections in the blood donor population and therefore the safety of the collected donations and the recipients. Among all the transfusion transmissible infections tested in the present study, incidence of HBV was found to be the highest. Prevalence of Transfusion transmissible infections was higher in men than women and in donors

belonging to age group of 20-39 years (reproductively active age group).

Blood transfusion is a life saving procedure and safety of blood and blood products is of utmost importance. Morbidity and mortality resulting from transfusion of infected blood has dire consequences not only for the recipient, but also for his or her family, community and the wider society. Prevalence of Transfusion transmissible infections was lower in voluntary donors than in replacement donors in our study. Therefore, regular, voluntary, unpaid donors are the safest group of donors. However, many a times individuals are forced to donate as replacement donors for want of blood for their relatives. Therefore, it is of utmost importance to continue screening donated blood with highly sensitive and specific tests and to counsel donors who are positive to any of the infections.

Conflict of Interest: None declared.

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ORIGINAL ARTICLE

Clinicopathological Analysis of Patients with Breast Cancer and Their Families

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ABSTRACT

Background: Breast cancer is one of the most common malignancies among Iranian women; however, its clinicopathological feature is uncertain. We pioneered a genetic counseling program among patients with breast cancer and their families in Isfahan. This is the first report of this program.

Methods: This was a descriptive cross-sectional study on women with breast cancer registered in Ala Cancer Control and Prevention Center (ACCPC)during 2014. The women and/or their first/second relatives were enrolled for genetic counseling, then their demographic and clinicopathological data were analyzed using SPSSsoftware.

Results: The records of 258 patients with breast cancer and their families were studied. The mean age of the patients at diagnosis was 44.2 years (range: 25-71 years). Of these, 88 (34.1%) patients had ≤40 years at diagnosis. Only 2 (0.8%) patients were men. Also, 21 (8.1%) out of the 258 patients had died at the time of genetic counseling. Distant metastasis was found in 40 (15.5%) patients at diagnosis. The most common pathological feature of breast tumor was invasive ductal carcinoma (68.2%) and the rarest were sarcoma (0.4%) and papillary carcinoma (0.4%). Triple-negative molecular phenotype breast cancer was reported in 25 (9.7%) patients. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) were negative in 32.2%, 27.1%, and 44.2% of the patients' tumors, respectively. P53 had been checked in 41.5% of the patients of which about 70.1% were mutant. Overall, 895 cases of cancer were reported among the patients and their families (3.5 patients per family: range=1-9) of which breast, gastric, and colorectal cancers with an incidence of 43.9%, 8.3% and 5.5%, were the most common malignancies, respectively.

Conclusion: Early-onset breast cancer and positive family history for cancer were seen in a significant proportion of the patients in our center, indicating the importance of genetic counseling among the patients and their families.

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Introduction

Cancer is the third cause of death after ischemic heart disease and accidents among the Iranian population.[1] Breast cancer (BC) is the most common cancer in women throughout the world.[2-4] In our country, BC is the most common cancer and the fifth most common cause of death among women.[5]

The number of women affected by BC has been reported to be 1.7 million in 2012, with 6.3 million affected women within the previous five years.[6] Moreover, BC has been

reported as the most common cancer among women in countries in the Eastern Mediterranean Region.[7] More than one million cases of BC occur worldwide every year, of which about 580,000 cases occur in developed countries (>300/100 000 population per year) and the remainder in developing countries (usually <1500/100,000 population per year), despite their much higher overall population and younger age. In 2000, the year for which global data exists, some 400,000 women died from BC, representing 1.6% of all female deaths. The proportion of deaths due to BC was far higher in developed countries (2% of all female deaths) than in developing countries (0.5%).[7] BC is a disease with high cost and expensive treatments which imposes a significant burden on health system of the world-wide countries.[8]

Treatment of BC in Iran is very expensive because the age of patients in Iran is about one decade less than Western countries, so the burden of the disease in Iran is likely to be considerably high.[8] Meanwhile, no comprehensive systematic screening and surveillance program has been set up to promote early detection and diminish the occurrence of BC among Iranian women. There are some dispersed local programs throughout the country, one of which is running in Ala Cancer Control and Prevention Center (ACCPC), Isfahan, Iran. In this study, we assessed some clinicopathological aspects of the registered patients in this center.

Methods

This was a descriptive, cross-sectional study carried out at ACCPC, a health promotion and palliative care clinic in Isfahan, central Iran, in which all specialities including psychology, palliative care, genetics, nutritional counseling and social workers are voluntarily serving cancer patients and their family members. Inclusion criteria were age at diagnosis of ≤50 years and/or a positive family history for any type of cancer regardless of the age at diagnosis. During the counseling, the familial pedigree was drawn. The clinicopathological features of patients with BC were analyzed using SPSS 19 software.

Results

The records of 258 patients with breast cancer and their families were studied. The mean age of the patients at diagnosis was 44.2 years (range: 25-71 years). 88 (34.1%) patients had ≤40 years of age at diagnosis. Only 2 (0.8 patients %) were men. 21(8.1%) patients out of 258 had died at the time of genetic counseling. 50.4% of breast tumors were located on the left side, 46.1% of the right, and 3.5% on both sides. The most common pathological feature of BC was invasive ductal carcinoma (68.2%) and the rarest were sarcoma (0.4%) and papillary carcinoma (0.4%) (table 1). 96.5% of tumors were unifocal and 3.5% were multifocal. Radical mastectomy, total mastectomy and partial mastectomy were performed for 38.0%, 25.6%, and 36.0% of the patients, respectively. Averagely, 5.9 lymph nodes per case had been resected during surgery of which 2.7 were involved. Metastasis was seen in 40 (15.5%) patients at diagnosis of whom 12 cases were ≤40 years of age and 28 cases were >40 years of age at diagnosis. Bone, liver, lung and brain were the most frequent metastatic sites with an incidence of 57.5%, 35.0%, 32.5%, and 17.5%, respectively. Triple-negative molecular phenotype was detected in 25 (9.7%) of the 258 patients. ER, PR and HER2 were positive in 67.8%, 48.8%, and 31.8 % of the tumors, respectively.

Table 1: Frequency of Pathologic features of breast tumors according to their diagnostic reports

Pathology	Frequency	Percent
Carcinoma in situ	26	10.1
Infiltrative Ductal Carcinoma	176	68.2
Infiltrative Lobular Carcinoma	26	10.1
Mucinous	3	1.2
Medulary	2	0.8
Sarcoma	1	0.4
Papillary	1	0.4
Otther	8	3.1
Mixed	13	5
Unknown	2	0.8
Total	258	100

P53 was evaluated in 41.5% of the patients, of which 29.9% were mutant. The mean age at diagnosis in patients with mutant and wild-type P53 tumors was 45.8 and 44.2 years, respectively. Moreover, 2 (6.3%) out of 32 patients with BC with mutant P53 versus 14 (18.7%) out of 75 patients with wild-type P53 had metastasis at diagnosis (table 2).

We also found a positive family history of cancer among 86.7% and 62.5% of the patients with wild-type P53 tumors and those with mutant P53, respectively. Altogether, 895 cases of cancer (range: 1-9 per family) were found including the patients and their families, of whom 589 (65.8%) cases were found in women. In the women, breast, uterus and colorectal cancer with an incidence of 65.2%, 5.1%, and 3.9% were the most common observed malignancies, respectively. The corresponding figures for men was gastric, prostate, and lung cancer with an incidence of 18.0%, 11.8%, and 10.5%, respectively (table 3).

Table 2: Frequency of hormone receptors and biomarkers in breast tumors according to their immunohistochemical staining

Biomarker	Positive		Negative		Unchecked	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
ER	175	67.8	83	32.2	0	0
PR	126	48.8	70	27.1	62	24.0
HER2	82	31.8	114	44.2	62	24.0
P53	32	12.4	75	29.1	151	58.5

Table 3: Frequency of cancer sites among family members of breast cancer patients.

Cancer site	Gender		Total
	Male	Female	
Breast	9	384	393
Stomach	55	19	74
Colorectal	26	23	49
Brain	29	17	46
Lung	32	14	46
Leukemia	22	19	41
Prostate	36	1	37
Uterus	1	30	31
Liver	15	10	25
Bone	14	6	20
Larynx	13	3	16
Lymphoma	8	7	15
Bone marrow	5	9	14
Ovarian	0	11	11
Skin	5	1	6
Thyroid	1	4	5
Pancreas	2	3	5
Gall-bladder	0	5	5
Bladder	3	2	5
Small bowell	4	0	4
Testis	2	1	3
Kidney	0	2	2
Nasopharynx	1	1	2
Retinoblastoma	2	0	2
Sarcoma	0	1	1
Unknown	19	16	35
Total	306	589	895

Discussion

Incidence rate of BC is estimated to be 22–24 per 100,000 among Iranian female population which is about one fourth of that in developed countries.[5,9] Iranian women are afflicted by BC at least one decade earlier compared with western countries.[10] Mean age of BC in western countries has been estimated to be about 63 years of age.[11] Some recent studies show that BC has a lower incidence among Iranian women than other developing countries. These studies also show a general growing trend in the 45–49 year-old age group with a decreasing trend for women older than 49 years.[12] We found 44.2 years of age to be the mean age of diagnosis in our population. The peak occurrence of BC was among 40-50 year-old age group. In 32.2% of our patients, the age was less than 40 years at diagnosis. Given the inclusion criteria to select high risk patients with BC including early-onset disease and/or a positive family history for cancer, we expected a lower age at diagnosis in the patients. Comparing our findings with similar Iranian studies, we could not find a distinct gap in this matter. Harirchi and coworkers also found a mean age of about 47 years in 903 patients with BC.[13] This shows a significant proportion of the Iranian patients with BC belong to the early-onset group indicating the importance of screening programs among Iranian young women (figure 1).

We found that 50.4%, 46.1% and 3.5% of the breast tumors to be on the left, right and both sides, respectively. This finding is consistent with previous epidemiological findings reported in the Iranian population. In a large study on 2343 BC patients from five hospitals in Tehran, during 1996-2000, 51.7% and 47.1% of e thtumors were located in the left and right breast, respectively. Also 1.5% of tumors were bilateral.[14] BC was more common in the left breast according to other studies.[15,16] Although the nature of this difference is not clear, the left breast is somewhat larger than the right, and this may explain the higher incidence of BC on left side.[17]

We found invasive ductal carcinoma was the most common pathology among our patients with an incidence

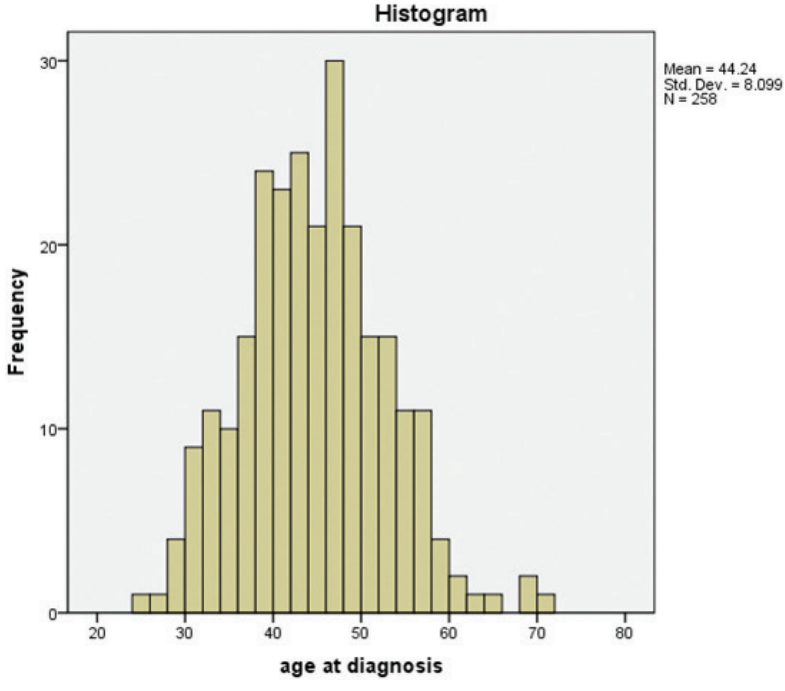

Figure 1: Distribution of breast cancer patients according to mean age at diagnosis.

of 68.2% of 68.2%. It is slightly lower than what is reported in other Iranian studies. According to an epidemiological review among Iranian studies throughout the country, 77% of BC tumor types were reported to be invasive ductal carcinoma.[9] More than 10% of the studied patients in our study were reported as lobular carcinoma, while in similar studies from Iran, different frequencies ranging from 1.9% to 11.6% have been reported for this pathological feature.[9] Moreover, we also found some rare types of breast pathologies such as sarcoma and papillary carcinoma.

Radical and total mastectomy was performed for 38.0% and 25.6% of the patients, respectively; while 36% of the patients underwent partial mastectomy. In a recent study from Isfahan on 119 patients with BC, partial mastectomy was performed in 32.5% of the cases. The patients who had endured partial mastectomy showed more satisfaction and fewer complications than those who had underwent total mastectomy.[18] A cross-sectional study from Iran evaluated the preference of general surgeons toward breast-conserving surgery versus total mastectomy. Breast-conserving surgery techniques were preferred by 19% of the surgeons in their routine practice.[19] In fact, most of the surgeons have more desire to do total mastectomy in order to avoid recurrence of the disease. Some studies have shown an equal incidence rate for recurrence in both techniques. Accordingly, some of the mastectomy surgeries must be changed to breast-conserving methods to prevent psychococial and physical complications.[20,21] It suggests the importance of an exact recurrence risk assessment among patients with BC and hence consider the best option.

The metastatic rate of BC at diagnosis was 15.5% in our study. According to review of the literature, 6% of BCs are averagely metastatic at diagnosis.[22,23] Meanwhile, some larger Iranian studies have shown more frequent advanced BC among Iranian women than developed countries. The exact rate of metastasis at diagnosis.[9,24] It seems that the incidence of advanced BC among Iranian women is more than developed countries. It indicates the necessity of screening for early detection of BC, particularly among the high risk families. We found that the bone with 53.3% was the most frequent metastatic site. Our statistics in this regard was similar to other studies from Iran and other countries,[25,26] indicating the importance of performing bone scan in thestaging of the patients. In total, about 70% of patients with metastatic breast cancer develop bone metastasis. Bone is the most common site of metastasis in BC and the most common site of recurrence in 30%–40% of the cases.[27] Meanwhile, the patients with only bone metastasis have a better prognosis than those with visceral metastasis to the liver, lungs, or brain.[28-30]

In our study 10.2% of the BC patients showed triple-negative BC (TNBC) molecular phenotype in which ER, PR and HER2 were negative. Given the epidemiology of TNBC, our results were similar to other studies.[31,32] Reportedly, 10-15% of all patients with BC show the TNBC phenotype.[33] However, there are some limited evidences of higher frequency of TNBC than other subtypes of BC among Iranian women.[34] Since the prognosis among TNBC cases is poorer than other BC subtypes[32,35], this group of patients needs more attention during post-surgical period in terms of recurrence.

P53 was mutant in 30% of the BC tumors in our study. This findig is consistent with most of the other studies, that have reported P53 mutation in about 20-40% of aggressive breast cancers.[36,37] In a recent study on 104 Iranian patients with BC, 28.8% showed P53 mutant phenotype.[38] In another Iranian study, 29 (40.3%) of the 43 BC samples showed P53 mutations.[39] Although in some studies, patients with BC with mutant P53 tumors have had more age at diagnosis in comparison to patients with wild-type P53.[38,39], we find no significant difference between them. The proportion of high histologic grade in P53 mutant tumors to P53 wild-type tumors in our study was more than two fold. According to many studies, the BC tumors with mutant P53 are usually more aggressive than those with wild-type P53 and are identified as high histopathological grades at diagnosis.[39-41] Positive cancer family history was more frequent among our BC patients with wild-type P53 tumors than those with mutant P53 (86.7% versus 62.5%). There are some discrepancies in this regard according to different studies.[38,42] The fact around which there are yet some active research area.

We found 895 cancer patients in pedigrees related to 258 BC patients. In the other words, about 3.5 cancer patients was registered for each BC patient. As was expected, nearly two-thirds of all cancer patients were female. If we subtract 258 BC patients from 895 cancer patients, we obtain 637 including both male and female affected members among our BC patients' families. Accordingly, the proportion of male to female in cancer patients would be 304/333. Meanwhile, this proportion in Iranian general population has been estimated about 1.12 according to recent studies.[5,43] It means that in families of BC patients, females are likely at more risk to develop cancer. Breast, uterus and colorectal cancer among women and gastric, prostate and lung cancer among men were the most frequent cancers, respectively. According to the last report of Iranian health ministry, breast and gastric cancer are the most common cancers among Iranian women and men, respectively.[5] Similar pattern of cancer frequency between our patients and general population emphasizes the essential role of environmental factors in cancer development compared to hereditary predisposing factors for cancer.

Conclusion

Given the high frequency of early onset BC among Iranian women, necessity for a comprehensive, early-onset genetic counseling and screening program is undeniable. Exploring molecular and clinicopathologic features of breast cancer among Iranian populations could lead to promote all the preventive health-related interventions in this disease.

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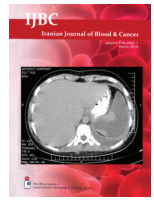

CASE REPORT

Splenic Infarction in a Case of Acute Promyelocytic Anemia

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ABSTRACT

Splenic infarction occurs due to occlusion of splenic vessels that leads to splenic tissue ischemia and necrosis. There are several reports regarding splenic infarction in patients with acute myelogenous leukemia (AML). Herein, we report a case of acute promyelocytic anemia (AML-M3) who presented with abdominal pain and splenic infarction.

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Introduction

Splenic infarction occurs due to occlusion of splenic vessels that leads to splenic tissue ischemia and necrosis.[1-4] There are several reports regarding splenic infarction in patients with acute myelogenous leukemia (AML). Here in, we report a case of acute promyelocytic anemia (AML-M3) who presented with abdominal pain and splenic infarction.

Case Presentation

The patient was a previously healthy 20-year-old woman who presented with blurred vision, abdominal pain and dizziness following hemorrhoid surgery. Physical examination revealed pallor, wide peripapillary retinal hemorrhage and splenomegaly. Blood examination on admission revealed: WBC; 54×10^9/µl, Hb;7 gr/dl and Platelet count;16×10^9/µl, LDH; 3300 IU/L (normal range up to 480), Prothrombin time (PT); 19.3 sec (12-15), INR; 1.67(1-1.2), Partial thromboplastin time (PTT); 28 sec (24-45), Fibrinogen level; 287 mg/dl (200-400), Fibrin degradation product (FDP)>20 mg/L (reference range less than 10 mg/L) and D dimer >2000 ng/ml (normal <255). The Patient underwent bone marrow aspiration and biopsy which revealed hypercellular marrow with more than 95% blasts and in spite of mostly abnormal promyelocytes compatible with AML-M3. Flowcytometry revealed blasts positive for CD33, CD117 and negative for HLA-DR, myeloperoxidase staining of the blasts were strongly positive. Molecular genetic study revealed PML-RAR-α positivity by RT-PCR. Abdominal ultrasound showed splenomegaly (spleen size: 165×90 mm) with heterogeneous echo and large peripheral hypoechoic geographic lesions suggestive for infarction. Abdominal spiral CT scan showed splenic enlargement with extensive peripheral hypodensity and lack of contrast enhancement in favor of infarction (figure 1). Chemotherapy with daunorubicin, All-trans retinoic Acid (ATRA) and arsenic trioxide was initiated for the patient. He also received FFP and platelet transfusions considering the patients' conditions and diagnosis of the patient. Initially, the

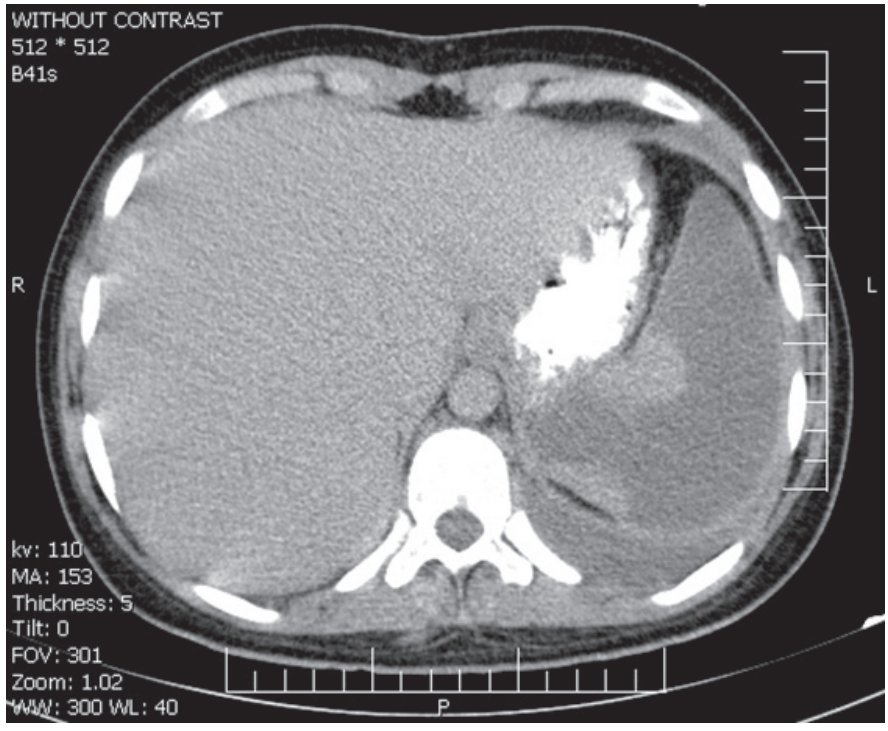

Figure 1: splenomegaly with extensive hypodensity in favor of splenic infarction.

patient underwent supportive care and close observation for management of the splenic infarction. Finally, surgical consultation was conducted on day 28 after induction of remission which splenectomy was recommended due to persistence of large splenic lesions on serial abdominal imaging but did not perform due to thrombocytopenia.

Discussion

In our patient with AML-M3, disseminated intravascular coagulation (DIC) in the spleen led to splenic infarction. Splenic infarction is defined as occlusion of the splenic vessels that leads to splenic ischemia and necrosis which may be total or segmental. A heterogenous group of diseases cause splenic infarction, mostly attributable to hematological malignancies and myeloproliferative disorders. However, benign hematological disorders such as autoimmune hemolytic anemia, hypercoagulable states, vascular disorders, trauma and iatrogenic etiologies such as pancreatectomy and liver transplant can also be influential.[1-8] Acquired protein C deficiency has been reported in AML.[9,10] Splenic infarction alone is not an indication for surgery and requires close follow-up. Surgery is indicated for persistent symptoms or subsequent complications such as hemorrhage, rupture, and abscess formation. Our explanation for splenic infarction in this case of AML-M3 was thrombotic complication due to AML and its inherent thrombotic tendency as disseminated intravascular coagulation.

Conflict of Interest: None declared.

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Letter to Editor

Osteoblasts in the Vicinity of Osteoclasts in a Case of Infantile Osteopetrosis

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Dear Editor

An 18-month-old girl with failure to thrive, frontal bossing, bilateral proptosis, profound hepatosplenomegaly, severe anemia and thrombocytopenia was admitted to our pediatric oncology department. On physical examination she was a fussy baby with malformed teeth and abdominal distension. There was complete visual loss in the child. Laboratory data showed severe anemia, normal leukocyte counts with leukoerythroblastosis, and moderate thrombocytopenia (platelet counts 57000 /μL). Liver transaminases were three times the normal values. Hemoglobin electrophoresis was normal. Skeletal survey showed remarkable sclerosis of the base of the skull, bone within bone appearance in vertebrae and metaphyseal fraying and cupping in distal long bones of the extremities which were all in favor of osteopetrosis. Bone marrow aspiration of the infant revealed a mild to moderate hypocellular marrow. There were increased number of osteoclasts (about 5 osteoclasts per 500 cells) observed in high power fields (×100). There were also osteoclasts with increased size and nucleation noticeable in some occasional fields (figure 1, 2). Another noticeable finding which prompted us to report this case was the simultaneous increase in the number of osteoblasts along with osteoclasts; some even close together in the same field (figure 2, 3).

Osteopetrosis, or marble bone disease, was initially reported by Albers-Schönberg in 1904 as a complex disease associated with disrupted physical development and bone fragility.[1] The disease ranges from mild to severe lethal states. It is genetically determined as either an autosomal dominant benign type or an autosomal recessive malignant type.[2] A defect in the mechanism of bone remodelling leads to a constellation of somatic problems and hence devastating clinical picture of the disease. The basic defect in bone formation and resorption resides in osteoclastic malfunction that in turn results in an increase in bony mass, thickening of the cortical bones, and narrowing or obliteration of the medullary cavities.[3] Multiple genetic mutations contribute to developing this heterogeneous disease. The pathogenetic defect may be intrinsic either to the osteoclast lineage or to the mesenchymal cells that constitute the microenvironment supporting the development and activation of the osteoclasts.[4] Osteoclasts are the cells responsible for bone resorption that work continuously in conjunction with osteoblasts to proceed with bone strength and function.[2,4]

Colony stimulating factor 1 (CSF-1), the growth factor for cells of the mononuclear phagocytic system, is essential for the development of osteoclasts. Altered CSF-1 production has been considered to be involved in almost complete lack of osteoclast development and as a result impaired bone resorption.[4] In a study, light and transmission electron microscopic study of iliac crest metaphyseal bone from nine patients with infantile osteopetrosis demonstrated a variable spectrum

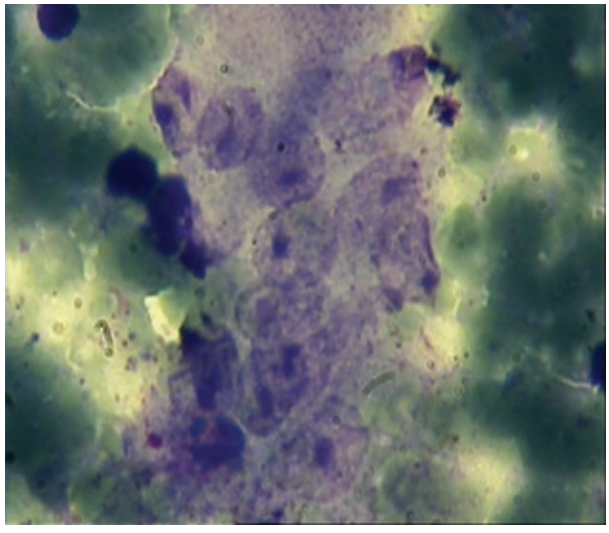

Figure 1: A large osteoclast with increased nucleation

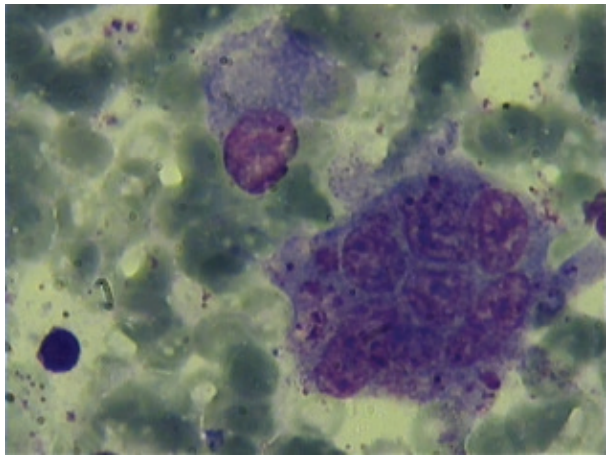

Figure 3: Osteoclast along with osteoblast in a smear

of osteoclast abnormalities; osteoclast numbers were invariably increased.[5] Osteoclast number, size, and nucleation ranged from mildly to markedly increased. In those with only a mild-to-moderate osteoclast increase, the marrow had a near-normal appearance with a good complement of hematopoietic cells. In those with markedly increased osteoclasts (hyperosteoclastic state) there were only scanty nests of hematopoietic cells.[5] Osteoclasts are only infrequently seen in bone marrow aspirates. They become more obvious when the cellularity is depressed.[6] In our case there was increased number of osteoclasts easily recognized on marrow smears. It has been shown that in both autosomal recessive and dominant types of osteopetrosis with different mutations bone resorption can be severely hampered despite marked elevation in osteoclast number.[7] According to the study by Henriksen et al, in osteopetrosis, resorption is severely reduced, but the osteoclast number was increased by two to three-fold.[8] Osteoblasts might also affect the pathogenesis of the disease, either because they are affected by intrinsic defects, or because their activity may be enhanced by deregulated osteoclasts present in large quantities in most forms.[9] However, interestingly in the presented case osteoblasts were also increased in number.

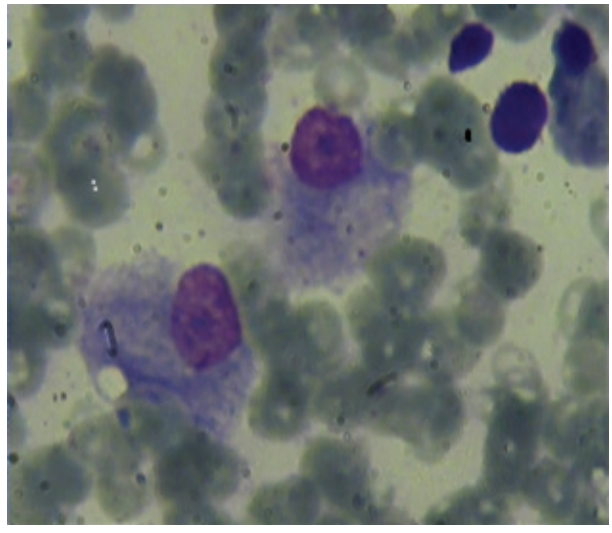

Figure 2: Increased numbers of osteoblasts

Finally, a combined defect in osteoblasts and osteoclasts in terms of number and function could be hypothesized that needs to be proved in future.

Conflict of Interest: None declared.

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Letter to Editor

Is Medical Application Software a New Strategy for Oncologists?

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Dear Editor

Electronic medical applications on cell phones or tablets in the field of oncology have resolved the need of today's oncologists. We consider new strategies for the management of chemotherapy and infections or other problems in oncology wards using online publications and drugs, patient imaging and lab data through their integeration on electronic devices. Traditionally, oncologists have lost time searching for publications and were unable to benefit from online evidence-based bedside management.[1]

We began using high-technology cell phone application as smart phone format and personal computer tablets that offered us all the tools we needed as we did our clinical rounds in Amir Oncology Hospital. These tools were designed specifically for oncologists and oncology nurses. Some benefits of these applications were as follows:[1-3]

1.Better clinical assessment
2.Medication information availability
3.Order forms of management (adverse reactions, dose adjustment)
4.Access to information of different diseases
5.Consultation and interaction with physicians by Viber, What'sapp or other information interchange utilities
6.Chemotherapy protocol availability and true drug administration
7.Online Up-to-Date publications access and evidence-based treatment planning

Moreover, the top 11 oncology applications were as follows:[4]

1. **Cancer Rx**: It is used to search the latest drug and genetic information of four major types of cancer: breast, lung, melanoma, and colorectal cancer.
2. **Browzine**: Facilitates finding, reading, and monitoring thousands of scholarly journals available from university or college libraries, or through Open Access publishers from all disciplines.
3. **Draw MD Pediatrics**: It allows you to easily annotate any condition on pertinent medical illustration and you can easily upload your images.
4. **Micromedex**: Used for retrieving drug information
5. **QXMD CALCULATE:** Used in clinical practice to impact diagnosis, treatment, or determining prognosis._
6. **Jhon Hopkins ABX guide:** It features up-to-date, authoritative, evidenced-based information about treatment of infectious diseases to help you make clinical decisions. The guide breaks down details of diagnosis, drug indications, dosing, pharmacokinetics, side effects and interactions, pathogens, management, and vaccines.
7. **Pubmed on Tap**: Searches PubMed and PubMed Central publications.
8. **NCCN guidelines:** Prepares the Virtual Library of NCCN Guidelines® Formatted for iPad.
9. **Medscape:** Used by physicians, medical students, nurses.
10. **Inpractice oncology:** It is an iPad application, in the

field of oncology and hematology as a complete textbook for treating cancers. The content is broadly includes breast, lung, and hematological cancers, sarcomas, supportive care, and general oncology topics. Links to PubMed abstracts for cited literature are given within the text. Users can bookmark individual pages within the application, and can also email links to specific pages of the textbook.

11. **OHMD:** It is a secure-messaging platform between doctors and patients that integrates with electronic medical records on the provider's side.

Also, the *American Society of Clinical Oncology* (ASCO) has introduced the top 10 applications for mobiles that help access information such as iPlanner, ASCO iMeeting, ASCO Journals, and Cancer Net.

Finally, we believe that electronic medical devices facilitate physician access to necessary online information for evidence base patient management.

Conflict of Interest: None declared.

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