Trend in the presentation of cervical cancer in Nigeria

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Cervical cancer is the second leading cause of cancer deaths among women, and the most common gynecological malignancy.[1] Every year approximately 500,000 new cases are diagnosed globally with approximately 274,000 deaths. Over 80% of the new cases and approximately 85% of deaths occur in the developing countries of the world. In developed countries, there has been a continuous decline in incidence and mortality from cervical cancer,[2] a report from the United States shows that cervical cancer is now the 12th common cause of cancer deaths.[3] This decline is mainly attributed to the establishment of organized screening programs for the detection of the premalignant lesions of the cervix, treatment, and adequate follow up of detected cases.[3] This study aims to find the trend in the presentation and mortality in our institution. Ethical approval was obtained from the institution's Ethics and Research Board. The records of all patients managed over a 10-year period (1997-2006) were retrieved from the medical records department of the hospital and findings were compared to a similar study carried out in the same institution 10 years earlier. The exclusion criteria were cases with incomplete medical information, and cases where the diagnoses were not confirmed by histopathological analysis.

The socio-demographic parameters such as age, number of sexual partners and parity, as well as clinical information (**Table 1**) such as presenting symptoms, stage, and histological type was retrieved from the case files, and entered into a proforma prepared for the study. All the data were analyzed using SPSS version 11 for Windows. Percentages and means were calculated. The stages of presentations were compared with previous report. Chi square test was used to test for association. Over this 10-year period 122 patients who presented with biopsy-proven cervical cancer were managed and compared with 116 in the previous study. There were no statistically significant differences in the socio-demographic characteristics of the patients in both studies. The mean age of the patients was 52.6 years (29 to 85) years. In the present study, a total of 34 patients died of uncontrolled hemorrhage and renal failure while on admission compared with 12 in the previous study. Eighty-eight patients (88) were referred for radiation therapy at the regional radiotherapy center, only one patient is recorded as having completed the treatment. None of the patients in present study were offered surgical treatment while in the previous study surgery was carried out for 18 of the patients implying early stages at presentations. The only statistically difference was in the stages of the disease at presentation. (χ^2 =11.498, df = 3, p=0.006). More patients presented with late disease in present study than in the previous study.

Table 1 - Clinical data.

Presenting symptoms	Frequency study (%) 2007		Frequency study (%) 1998	
Post coital bleeding	17	(13.9)	12	(20.0)
Intermenstrual bleeding	17	(13.9)	28	(77.0)
Post menopausal bleeding	57	(46.7)	48	(35.0)
Abnormal vaginal discharge	25	(20.5)	7	(67.0)
Urinary fistula	4	(3.3)	5	(4.2)
Others	2	(1.6)	1	(0.8)
Total	**122**	**(100.0)**	**116**	**(100)**
Stage at presentation				
1	4	(3.3)	10	(8.6)
2a	10	(8.2)	9	(7.8)
2b	13	(10.7)	6	(5.2)
3a	20	(16.4)	13	(11.4)
3b	57	(46.7)	43	(37.1)
4a	15	(12.3)	34	(29.0)
4b	3	(2.5)	1	(0.9)
Total	**122**	**(100.0)**	**116**	**(100)**
Histological type				
Squamous cell carcinoma	117	(95.9)	113	(97.5)
Adenocarcinoma	5	(4.1)	3	(2.5)
Total	**122**	**(100.0)**	**116**	**(100)**

Despite the enormous resources and the wide publicity given to maternal mortality, HIV/AIDS adolescent contraception and abortion-related issues, no progress has been made in cervical cancer in many developing countries. Findings from this comparative study showed that no progress has been made in cervical cancer in terms of incidence and mortality as the incidence instead of falling has shown a slight increase. Late presentation is still common as most of the patients in our institution presented with advanced stages of the disease. Many African countries including

Nigeria lack both the capacity and the means to manage cancer effectively. With late presentations, most patients can only be managed with radiation therapy but these services are poorly developed. Nigeria has only 4 radiotherapy centers. Many patients that presented to these centers do not get treatment, due to the cost and the long waiting list before they succumbed to the disease. Hence, the need to emphasize prevention of the disease through screening, public education, and enlightenment should also be stressed as there is low level of awareness among the populace about cervical cancer.[4] Health workers also should be trained on the appropriate management of cervical pre malignant lesions as most gynecologists in the country lack the knowledge about the use of colposcopy and outpatient management of cervical pre-malignant lesions.[5]

In conclusion, despite the declining incidence and mortality of cervical cancer in the developed countries, the incidence has shown a slight increase in our center with high mortality and late presentation of patients. There is an urgent need for screening services using low cost techniques that would reach more people especially the underprivileged, as well as prompt treatment of detected cases. The limitation of this study was that, being a retrospective analysis data collection was incomplete and there was poor documentation.

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Prophylactic effects of *Echinacea purpurea* polysaccharide against lethal ocular herpes simplex virus type I

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Herpes Simplex Virus Type-1 (HSV-1) ocular infections are among the most prevalent viral eye infections worldwide and a major cause of virus-induced blindness. Due to therapeutic limitation of nucleoside analogs, there are ongoing investigations for newer anti-HSV agents, alternative to the nucleoside analogs. Recently, an increase interest has been observed in natural medicine with immunotropic activity and increasing cellular and humoral immunity against pathogens. *Echinacea purpurea* extract has been used in prophylaxis and therapy of various viral infections mainly the respiratory tract infections in animals and humans. In addition to antiviral properties, *Echinacea* extract has markedly displayed the immunostimulatory effects on mouse immune system.[1] The polysaccharide fraction derived from *E. purpurea* has been consistently found to have potent immune activating properties.[1] In this study, we assessed the effect of Echinacea polysaccharide (EP) fraction on protective effects when used before lethal ocular HSV-1 infection. This study was performed in January 2005, in Tarbiat Modares University, Tehran, Iran. The extract was prepared from Zardband Pharmaceutical Company (Tehran, Iran). Appropriate amount of extract with 2 control groups was applied in 3 groups. Virulent HSV-1 strain as an ocular challenging virus, and standard strain of herpes simplex virus type 1 (KOS) strain of HSV-1 as a positive control were used in this study. Echinacea polysaccharide fraction isolated from *Echinacea purpurea* aerial parts was supplied by Zardband Pharmaceutical Company (Batch No: E.PC04-L002-82) at a concentration of 20mg/ml. Polysaccharides was controlled for quality using thin layer chromatography (TLC) and densitometry (data not shown).

Four to five-week-old female albino mice were purchased from Razi Vaccine and Serum Research Institute of Iran (Karaj, Iran) with an average weight of 20g. All experiments were carried out according to the Animal Care and Use Protocol of Tarbiat Modares University, Tehran, Iran. The mice were separated in 3 experimental groups and the first group was inoculated 2 times with 100ml of inoculum containing 10^5 Pfu of live KOS strain of HSV-1 intraperitoneally on days 0 and 21. The second groups of mice were inoculated with phosphate buffer solution (PBS) as a negative control at the same manner. The last group of mice was inoculated

with 100mg of EP extract. Delayed-type hypersensitivity (DTH) and lymphocyte proliferation response to HSV-1 was tested 2 weeks after the last immunization in controls and test groups. Interferon-gamma (IFN-γ) protein level in supernatants of stimulated spleen cells was measured by ELISA, using a quantitative sandwich enzyme immunoassay technique (Quantikine Kits, R & D Systems, and Minneapolis, MN, USA). Three weeks after the last immunization, all mice were anesthetized by intraperitoneal injection of 100 mg/kg ketamine (Parke-Davis, Pontypool, UK) and 10 mg/kg xylazine (Bayer, Bury St, Edmunds, UK). Both corneas were lightly scarified using a 26 gauge needle. Then they were inoculated with 2 MLD50 of wild type virus in a volume of 25µl phosphate-buffer saline ($5x10^{5.5}$ Pfu /eye). The lids were held closed and gently rubbed for 30s. All of the mice were monitored for 25 days post challenge. Clinical evaluation of the infection was carried out as described previously, and same observer examined the eyes and scored the severity of epithelial lesions.[2] Mann-Whitney test was used to determine the significant ($p \leq 0.05$) difference in the disease severity scoring. A significant increase ($p \leq 0.05$) in the DTH and lymphocyte proliferation was evident in KOS and EP treated groups over that of negative control ones. Spleen cells of EP treated mice produced more IFN-γ in the culture than the cells from untreated mice. To determine the prophylactic effect of EP on the clinical evaluation after viral inoculation, 7 mice per group were used. The results showed that at 5th day of the infection a high percentage (6/7) of PBS in mice group experienced sign of keratitis and reached to (7/7) after 2 weeks. In sharp contrast, only 1/7 EP-treated mice exhibited clinical signs of scattered cellular infiltrate and edema in the cornea. These differences observed between EP and PBS treated mice were statistically significant while KOS group showed only moderate signs of infection in 1/7 of mice (Using Mann-Whitney $p \leq 0.05$) as shown in **Figure 1**.

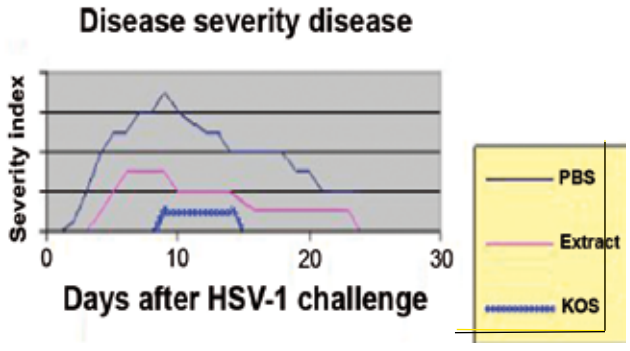

Figure 1 - Disease severity scoring over a 25-day post-infection in infected mice with 2MLD50 /eye. Disease severity throughout the observation period was significantly lower in mice treated with *Echinacea purpurea* than in phosphate buffer solution (PBS) injected mice.

To investigate protective efficacy, we evaluated whether immunological responses induced by EP could be correlated with protection against lethal ocular challenge. Echinacea polysaccharide activates macrophages to stimulate IFN-γ production in association with the secondary activation of T lymphocytes. The greater production of IFN-γ by spleen cells from EP-treated mice suggests that the injection of this extract would skew Th1/Th2 balance in favor of Th1.[3] To evaluate the influence of EP on protective efficacy, severity of corneal disease was determined. The results showed the decreased amount of severity in both KOS and EP-treated mice, while most of the control mice developed keratitis in the cornea.

These results indicate a positive correlation between KOS and EP groups in both developing protection against wild type HSV and stimulating immune responses. Despite of these cellular evidences of immunostimulation, pathways leading to enhance resistance to infectious disease have not been described adequately. In our study, this issue is the first report related to antiviral activity of EP against HSV-1 in BALB/c mice with systematic administration. Based on physical properties, polysaccharide should be a dominant immunostimulant component of the extract. When injected into mice, polysaccharide arabinogalactan isolated from *E. purpurea* was found to activate macrophages and was associated with an increased production of TNF-α, IL-1, and interferon β2.[4] Although based on the referred studies, it seems that no single agent or class of agents is solely responsible for all of the observed effects.[5]

In conclusion, this study confirmed previous findings and indicated the role of EP in stimulating the specific responses toward HSV infections. It is worth commenting that EP appears to be effective for prophylaxis and prevention from the severe ocular infection and reducing mortality rate in high risk individuals, so it can be exploited for development of an alternative remedy for HSV infections.

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Diagnostic value of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis

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Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting from 0.5-1% of the general population worldwide. The onset is most frequent during the fourth and fifth decades of life, with 80% of all patients developing the disease between the ages of 35 and 50. Recent studies show that joint injury in RA patients' progresses within 2 years from onset and aggressive treatment from the early stage can prevent the following progression of the disease.[1] The diagnosis of RA depends primarily on clinical manifestations of the disease. Up to 80% of patients with RA are rheumatoid factor (RF) seropositive, however, these antibodies are also present in relatively high percentages in other autoimmune diseases and infections, and even in healthy patients, particularly elderly individuals. So the presence RF is not specific for RA.[2] Nowadays, RF is the most popular laboratory test for diagnosis of RA. Fewer than one-third of unselected patients with a positive test for RF will be found to have RA. So, the RF is not useful as a screening test. However, the presence of RF can be of prognostic significance because patients with high titers tend to have more severe and progressive disease with extraarticular manifestations[2] than patients with low titers. Since the discovery of RF, more specific autoantibodies have been found in the sera of patients with RA. Antibodies against cyclic citrullinated peptide (anti-CCP) were first reported in 1998, and were found to have very high specificity.[2] It has more than 85% specificity, and at least 60-75% sensitivity for RA in some studies.[1-3] Because of this some rheumatologists put anti-CCP in variables of RA diagnosis.[2] Antibodies against cyclic citrullinated peptide can be detected at an early stage, even before onset of clinical symptoms of RA,[2,3] so it can be helpful in early diagnosis and treatment of RA, to prevent from progressive articular damages and complications. There is relationship between high titer of anti-CCP and joints erosion.[3] We undertook this study to assess on anti-CCP antibodies in 1) prevalence in RA patients, 2) the difference between seropositives and seronegatives, 3) predict of severity, and 4) relation by RF.

This cross-sectional study was conducted at Rheumatology Department of Hazrat Rasool Akram Hospital in Tehran, Iran over a period of 2 years from March 2004 to March 2006. One hundred eighty adult patients of documented RA with a disease duration of at least 2 years were included. Patients having an overlap of RA with other rheumatic diseases such as systemic lupus erythematosus (SLE), and systemic sclerosis were excluded from the study. Rheumatoid factor and anti-CCP antibodies were tested using a commercial enzyme linked immunosorbent assay (ELISA) kit. The blood samples were collected and stored to be analyzed in the same day. An anteroposterior view x-ray of wrist and hand was obtained. A rheumatologist, used a Larsen's modification score[4] to assess radiographic joint damage in a 0-I (mild abnormality), II-III (moderate abnormality), and IV-V (severe abnormality) scale in a blind fashion regarding serology and clinical status. We determined sensitivity, specificity, positive, and negative predictive values of anti-CCP in seropositive patients. t-test statistic was applied to describe variation between seropositive and seronegative patients in anti-CCP, and relation between RF and anti-CCP. To assess the effect of RF and anti-CCP in contributing to severity, patients were divided into 3 groups: Group I: RF+ CCP+, Group II: RF+ CCP- or RF- CCP+, and Group III: RF- CCP-. Association between categorical variables was carried out using the Chi-square test. Mann Whitney test was performed to analyze data that were not normally distributed. *P* value less than 0.05 was mentioned significance. All statistical tests were analyzed using the SPSS version 11 software. The study followed the Declaration of Helsinki. All the process was explained to the patients, likewise we did not carry out any extra interventions on them. Of the 180 patients, 84% (n=151) were women and 16% (n=29) were men. The seropositive (RF+) patients was 69 (38%) and seronegative (RF-) patients was 111 (62%). Of the 180 patients 93 (51.6%) tested positive

Table 1 - Characteristics and laboratory findings of patients

Characteristics	Seropositive (n=69)	Seronegative (n=111)	Tests used	*P*-value
Age (years)	47±8.6	51±6	Mann Whitney	>0.05
Disease duration (years)	5 (3-9)	4 (3-5)	Mann Whitney	<0.05
Anti-CCP +, (%)	55 (79.7)	38 (34.2)	Chi-square	0.000

Anti-CCP - anti cyclic citrullinated peptide antibodies

for anti-CCP antibodies. Demographic, clinical, and laboratory features of RA patients are shown in **Table 1**. Statistical values of positivity of anti-CCP in seropositive patients in this study are: sensitivity 79.7%, specificity 65.7%, positive predictive value 59.1%, and negative predictive value 83.9%. In wrist and hand x-ray evaluations between the 3 groups, the more radiographic damage (Larsen score IV-V), was seen in Group I compared to the others groups that this trend reached statistical significance (Chi square, $p<0.05$). The less damage was seen in group 3. Shankar et al[5] with a study on 211 RA patients in India found that anti-CCP antibodies were found to have a very high sensitivity and positive predictive value in predicting erosions in seropositive RA. Additionally, they had a good NPV in the seronegative subgroup, suggesting that if a patient is negative for both RF and anti-CCP, the chances of developing erosive disease are significantly lesser. Another study used that anti-CCP antibodies exhibit a better diagnostic value than RF, and a correlation with radiological joint damage, and therefore are useful in everyday rheumatology practice.[3] The sensitivity of anti-CCP was 51.6%, and RF was 38.3% in our study compared with other studies that anti-CCP had more sensitivity.[1,5] A good test for screening must have high sensitivity, so it seems that anti-CCP is better than RF in screening. A high sensitivity (79.7%), and negative predictive value (83.9%) of anti-CCP in seropositive patients show the correlation between 2 parameters. The anti-CCP was positive in 34.2% of seronegative patients in our study. This is near to other studies.[3] It means that some RA patients are RF negative but anti-CCP positive so anti-CCP is very important test in RA patients. Our study demonstrated a correlation between anti-CCP antibodies, and radiological joint score in patients with RA. Anti-CCP antibodies with RF was found to be associated with more radiological joint damage. In other study, the most severe joint damage was seen in RF+ CCP+[5] or CCP+ patients.[1,3] Our study have some limitations. Our study was cross-sectional, and we could not follow the patients for severity of joint damage. Likewise, joint damage in this patients probably depends on the quality of treatment,[5] so patients should be received same drugs and be followed.

In conclusion, our findings showed the correlation between anti-CCP and RF, and more prevalence of anti-CCP in seropositives. Anti-CCP with RF were strong predictors of erosive disease in RA patients. Their absence had a strong negative predictive value for erosive disease. For more reliable results, we suggest another prospective studies with more cases.

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