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CLINICAL AND PARACLINICAL MANIFESTATIONS IN CANCER PATIENTS REFERRED TO THE EMERGENCY ROOM OF ONE TERTIARY HOSPITAL IN NORTHERN IRAN

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Abstract – *Objective:* *An Emergency Department is one of the major places for quick access to the complaints of cancer patients. Most cancer patients referred to an Emergency Department at least once during their disease period. Therefore, the aim of this study is to determine the clinical and paraclinical manifestations in cancer patients referred to the Emergency Room of one tertiary hospital in northern IRAN in 2016.*

Patients and Methods: *This is a cross-sectional research on 140 patients with different cancers referred to the Emergency Room of one tertiary hospital in northern of IRAN in 2016. Age, gender, type of cancer, metastasis, type of treatment, and laboratory data were collected and recorded in the designed form. Data were then inserted into SPSS software and analyzed.*

Results: *The most clinical manifestations included pain (37.1%), nausea and vomiting (33.6%), and weakness and lethargy (30%). The most frequent cancers included colon cancer (26.4%), breast cancer (14.3%), and gastric cancer (12.9%), respectively. Among the clinical symptoms, fever was seen most in leukemia and lymphoma; ascites was seen most in colon, pancreas and breast cancers; nausea and vomiting were seen most in breast, gastric, colon and pancreas cancers; constipation was only seen in colon cancer; loss of appetite was seen most in gastric and esophagus cancers; pain was seen most in colon cancer and multiple myeloma; dyspnea was seen most in lung and breast cancers; weakness and lethargy were seen most in gastric and colon cancers. Loss of appetite in males and pain in females were significantly higher. Leukopenia and anemia were significantly higher in males.*

Conclusions: *Using preventative methods and providing patients with required training may be useful in alleviating onset of symptoms such as nausea and vomiting in patients, reducing the frequency of referral of patients to Emergency Departments, and lowering financial burden of treatment costs of the patients.*

KEYWORDS: *Cancer, Emergency Department, Symptoms.*

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INTRODUCTION

Cancer is the second most common cause of death after cardiovascular diseases in the world[1]. Cancer treatment includes chemotherapy, radiation therapy, and surgery. The major complications of cancer treatment are related to the complications of the methods. Chemotherapy-induced complications often cause severe negative side effects such as lowering the body's resistance to infection, internal bleeding, diarrhea, constipation, nausea, vomiting, alopecia, and anemia[2,3]. Although radiation therapy side effects are unpleasant, the complications are not often acute or dangerous and they are removed over time (a few weeks after completion of treatment). The complications depend on treatment method, therapeutic area, patient's tolerance, and the amount of radiation (radiation dose). The most common side effect of radiation is local burn. Of course, some general side effects, such as fatigue and depression, may occur during radiation. The Emergency Department is one of the most important places for quick access to the complaints of the patients. Most of the patients referred to an Emergency Department at least once during their disease period[4]. Numerous studies[1,4] have already been conducted on the evaluation of different aspects of the reasons for referral of cancer patients to Emergency Departments. Correct diagnosis and appropriate treatment of the patients in an Emergency Department may improve their quality of life and reduce mortality[5]. Cancer patients have some periods of chemotherapy performed, which are generally repeated every two to three weeks. As mentioned earlier, some complications such as fatigue, weakness, nausea, vomiting, loss of appetite, diarrhea, constipation, hair loss, weight loss, and dry mouth, used to occur[6]. Patients may not be aware of the side effects of chemotherapy and the way they are managed[7-9]. When patients experience such complications, they used to refer to an Emergency Department, which is considered a key level for differentiating outpatients and hospitalized patients[8]. The evaluation of the cancer patients, who refer to Emergency Departments, show that they might refer in connection with the disease itself or the non-specific symptoms related to other diseases or the complications caused by the treatment method of the patients[10-12]. With respect to cancer prevalence in Mazandaran Province, the increase of referral of this group of patients to the Emergency Departments of hospitals, and the necessity of an appropriate management for treating them, the present study is aimed to determine the clinical and paraclinical manifestations in cancer patients referred to the Emergency Room of one tertiary hospital in northern of IRAN in 2016.

PATIENTS AND METHODS

This is a cross-sectional study on the cancer patients referring to the Emergency Department of Imam Khomeini Educational and Therapeutic Center of Sari. The sample size was estimated on 140 individuals based on the similar studies and the application of the formula for calculating sample size. The cancer diagnosis was based on pathological evidence and oncologist confirmations. To observe Ethical Principles, patients became aware of the above study. They were invited to answer the questionnaire after showing their willingness and obtaining written consents. A general and complete examination and diagnosis measures were performed on all the included patients.

STATISTICAL ANALYSIS

After collecting the questionnaires and extracting data, descriptive statistics (mean, SD, and frequency) and analytical statistics (the X^2, *t*-test, and according to the values of $p < 0.05$) were used for data analysis. Data were analyzed through descriptive, in SPSS statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

140 cancer patients included in the study consisted of 74 males (52.9%) and 66 females (47.1%). The mean age of the participants was 50.08±12.88. Table I shows the frequency of different types of cancers in the study patients. As showed in Table I, the maximum involvement was related to the colon (26.4%), breast (14.3%), and gastric (12.9%). Table II shows the frequency of site of metastasis in the study patients. Maximum metastasis was observed in liver (34.1%), brain (15.9%), and bone (13.6%). The study showed 44 patients (35.7%) with metastasis. The previous treatment on patients including chemotherapy, surgery, and radiotherapy was performed in 97.1%, 64.3%, and 16.4 of patients, respectively. The maximum clinical manifestations included pain (37.1%), nausea and vomiting (33.6%), and weakness and lethargy (30%). Table III compares clinical manifestations of patients when referring to the Emergency Department based on gender. As showed in the table, loss of appetite in males and pain in females were significantly higher. Other symptoms were not different in males and females; however, weakness and lethargy were rather higher in males. Table IV compares the clinical manifestations of the patients when referring to the Emergency Department based on age. As showed in the table,

TABLE 1. Frequency of cancer type in patients when referring to the Emergency Department.

Type of cancer	Frequency	Percentage
Bladder	2	1.4%
Hepatocellular carcinoma	2	1.4%
Renal cell carcinoma	2	1.4%
Uterus	3	2.1%
Ovary	4	2.9%
SCC	4	2.9%
Osteosarcoma	4	2.9%
Esophagus	5	3.6%
Multiple myeloma	6	4.3%
Lung	7	5%
Lymphoma	8	5.7%
Pancreas	8	5.7%
Leukemia	10	7.1%
Gastric	18	12.9%
Breast	20	14.3%
Colon	37	26.4%
Total	140	100.0%

TABLE 2. The frequency of site of metastasis in patients when referring to the Emergency Department.

Site of metastasis	Frequency	Percentage
Ovary	2	4.5%
Kidney	2	4.5%
Lung/liver	2	4.5%
Bone/Liver	2	4.5%
Lung	4	9.1%
Peritoneum	4	9.1%
Bone	6	13.6%
Brain	7	15.9%
Liver	15	34.1%
Total	44	100.0%

constipation and loss of appetite had significantly a lower mean age and weakness and lethargy had a higher mean age. Table V shows the relations between the clinical manifestations in patients when referring to the Emergency Department and type of cancer among the study patients. Based on the table, fever was seen most in leukemia and lymphoma, ascites was seen most in colon, pancreas and breast cancers, nausea and vomiting was seen most in breast, gastric, colon and pancreas cancers, constipation was only seen in colon cancer, loss of appetite was seen most in gastric and esophagus cancers, pain was seen most in colon cancer and multiple myeloma, dyspnea was seen most in lung and breast cancers, and weakness and lethargy were seen most in gastric and colon cancers. Table VI shows the relations between the clinical manifestations in patients when referring to the Emergency Department and site of metastasis in the study patients. Based on the table, there were significant relations between all the clinical manifestations and types of metastases, as fever, ascites,

TABLE 3. Comparison of the clinical manifestations of patients when referring to the Emergency Department based on gender.

Clinical manifestations	Males		Females		Total		p-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
Constipation	5	50.0%	5	50.0%	10	7.1%	0.851
Ascites	6	50.0%	6	50.0%	12	8.6%	0.836
Dyspnea	6	46.1%	7	53.9%	13	9.3%	0.611
Fever	14	63.6%	8	36.4%	22	15.7%	0.270
Loss of appetite	21	72.4%	8	27.6%	29	20.7%	0.045
Weakness and Lethargy	27	64.2%	15	35.8%	42	30.0%	0.076
Nausea and vomiting	26	55.3%	21	46.7%	47	33.6%	0.678
Pain	16	30.7%	36	69.3%	52	37.1%	<0.001

TABLE 4. Comparison of the clinical manifestations of the patients when referring to the Emergency Department based on age.

Clinical manifestations	Yes Mean and SD of age (in year)	No Mean and SD of age (in year)	p-value
Ascites	54 ± 8.90	58.46 ± 13.15	0.252
Constipation	49.70 ± 9.84	58.73 ± 12.89	0.032
Dyspnea	56.61 ± 9.23	58.23 ± 13.21	0.667
Fever	57.09 ± 15.22	58.27 ± 12.47	0.695
Loss of appetite	53.58 ± 13.91	59.26 ± 12.39	0.044
Nausea and vomiting	56.42 ± 15.39	58.92 ± 11.40	0.280
Pain	60.44 ± 12.11	56.77 ± 13.17	0.107
Weakness and lethargy	61.54 ± 13.27	55.60 ± 12.49	0.047

TABLE 5. Comparison of the clinical manifestations of the patients when referring to the Emergency Department based on the type of cancer.

Type of cancer	*Fever*	*Ascites*	*Nausea and vomiting*	*Constipation*	*Loss of appetite*	*Pain*	*Dyspnea*	*Weakness and lethargy*
Bladder	0	0	2 (4.3%)	0	0	0	0	2 (4.8%)
Breast	2 (9.1%)	4 (33.3%)	12 (25.5%)	0 (13.8%)	4	8 (16%)	4 (30.8%)	2 (4.8%)
Colon	2 (9.1%)	4 (33.3%)	9 (19.1%)	10 (100%)	3 (10.3%)	18 (36%)	0	11 (26.2%)
Esophagus	0	0	0	0	3 (10.3%)	0	0	5 (11.9%)
Gastric	0	0	10 (21.3%)	0	13 (44.8%)	2 (4%)	0	8 (19%)
Hepatocellular carcinoma	0	0	0	0	0	0	0	2 (4.8%)
Leukemia	10 (45.5%)	0	0	0	0	2	0	2 (4.8%)
Lung	0	0	0	0	0	1 (2%)	7 (53.8%)	0
Lymphoma	6 (27.3%)	0	0	0	0	0	0	2 (4.8%)
Multiple myeloma	0	0	0	0	0	6 (12%)	2 (15.4%)	2 (4.8%)
Osteosarcoma	0	0	0	0	0	4 (8%)	0	0
Ovary	0	0	0	0	0	4 (8%)	0	0
Pancreas	2 (9.1%)	4 (33.3%)	8 (17%)	0	2 (6.9%)	0	0	4 (9.5%)
Renal cell carcinoma	0	0	0	0	2 (6.9%)	0	0	0
SCC	0	0	0	0	2 (6.9%)	4 (8%)	0	0
Uterus	0	0	0	0	0	1 (2%)	0	2 (4.8%)
***p*-value**	**0.000**	**0.021**	**0.012**	**0.000**	**0.000**	**0.000**	**0.000**	**0.001**

nausea and vomiting, constipation, and weakness and lethargy were seen most in the patients with liver metastasis, pain and loss of appetite were seen most in the patients with bone metastasis, and dyspnea were seen most in the patients with lung metastasis. Table VII compares the laboratory findings of the patients when referring to the emergency department based on gender. It shows that leukopenia and anemia were significantly higher in males. Although neutropenia was only found in females, the difference was not significant. The laboratory findings of the patients show that 16.4% of the patients had anemia, 1.4% had neutropenia, and 5.7% had leukopenia. Table VIII compares the laboratory findings of the patients when referring to the emergency department based on age. As the table shows, anemia was found significantly in the older individuals and neutropenia was found in young individuals. Table IX shows the relationship between the laboratory findings of the patients when referring to the Emergency Department and type of cancer. As shown in the table, anemia was seen most in colon cancer, neutropenia in lymphoma, and leukopenia in leukemia. Table X shows the relationship between the laboratory findings of the patients when referring to the Emergency Department and site of metastasis. Anemia was seen significantly in liver, ovary, and kidney metastasis. No metastasis was found in the patients with neutropenia and leukopenia.

TABLE 6. Comparison of the clinical manifestations in the patients when referring to the Emergency Department based on metastasis.

Clinical manifestations	Bone	Liver	Lung	Brain	Ovary	Kidney	Perito-neum	Lung/ liver	Bone/ liver	p-value
Ascites	0	8 (66%)	0	0	0	0	0	2 (17%)	2 (17%)	0.001
Constipation	0	3 (100%)	0	0	0	0	0	0	0	0.022
Dyspnea	0	1 (17%)	4 (66%)	0	0	0	0	1 (17%)	0	0.000
Fever	0	4 (67%)	0	0	0	0	0	2 (33%)	0	0.014
Loss of appetite	5 (50%)	2 (25%)	0	0	0	0	2 (25%)	0	0	0.034
Nausea and vomiting	2 (7%)	13 (48%)	0	7 (25%)	0	2 (7%)	2 (7%)	0	2 (7%)	0.001
Pain	6 (50%)	0	2 (12.5%)	2 (12.5%)	2 (12.5%)	0	2 (12.5%)	0	0	0.000
Weakness and lethargy	0 (55%)	6	0	1 (9%)	0	2 (18%)	0	0	2 (18%)	0.010

TABLE 7. Comparison of the laboratory findings of the patients when referring to the emergency department based on gender.

Clinical manifestations	Males		Females		Total		p-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
Anemia (Hb<8 g/dl)	17	23%	6	9.1%	23	16.4%	0.027
Neutropenia (ANC<500)	0	0	2*	3%	2*	1.4%	0.131
Leukopenia (WBC<1000)	8	10.8%	0	0	8	5.7%	0.006

* Neutropenia with fever.

DISCUSSION

The Emergency Department is one of the most important places for quick access to the complaints of cancer patients. Most of the patients referred to an Emergency Department at least once during their disease period[4]. The present study aimed at discussing the clinical and paraclinical factors and manifestations in the cancer patients referring to the emergency department of Imam Khomeini Educational and Therapeutic Center of Sari. The most type of cancer among patients in this study was related to colon, breast, and gastric cancer; whereas, Norouzi nezhad et al[13], stated that the most common cancers in this Province among females were respectively breast, skin, and colon cancers and the most common cancers among males were respectively gastric, skin, and esophageal cancers. Other cases considered the major reasons for referring to the emergency

TABLE 8. Comparison of the laboratory findings of patients when referring to the Emergency Department based on age.

Clinical manifestations	Yes Mean and SD of age (in year)	No Mean and SD of age (in year)	p-value
Anemia (Hb<8 g/dl)	64.04±5.84	56.91±13.56	0.015
Neutropenia (ANC<500)	33±0.0	58.44±12.61	0.005
Leukopenia (WBC<1000)	55.25±14.06	58.25±12.84	0.523

TABLE 9. Comparison of the laboratory findings of the patients when referring to the emergency department based on type of cancer.

Type of cancer	*Anemia (Hb<8 g/dl)*	*Neutropenia (ANC<500)*	*Leukopenia (WBC<1000)*
Bladder	2 (8.7%)	0	0
Breast	0	0	0
Colon	12 (52.2%)	0	0
Esophagus	0	0	0
Gastric	1 (4.3%)	0	0
Hepatocellular carcinoma	2 (8.7%)	0	0
Leukemia	0	0	6
Lung	0	0	0
Lymphoma	2 (8.7%)	2 (100%)	2 (25%)
Multiple myeloma	0	0	0
Osteosarcoma	0	0	0
Ovary	0	0	0
Pancreas	2 (8.7%)	0	0
Renal cell carcinoma	0	0	0
SCC	0	0	0
Uterine	2 (8.7%)	0	0
***p*-value**	**0.000**	**0.004**	**0.000**

TABLE 10. Comparison of the laboratory findings of the patients when referring to the emergency department based on site of metastasis.

Clinical manifestations	*Bone*	*Liver*	*Lung*	*Brain*	*Ovary*	*Kidney*	*Perito-neum*	*Lung/ liver*	*Bone/ liver*	*p-value*
Anemia (Hb<8 g/dl)	0	2 (33.3%)	0	0	2 (33.3%)	2 (33.3%)	0	0	0	0.001

departments. Therefore, apart from skin cancer, it seems that the referral rate of patients to Emergency Departments is related to the overall rate of the prevalence of that type of cancer in the society. Maximum clinical manifestations in this study include pain, nausea and vomiting, weakness and lethargy, and loss of appetite; whereas, Wagner et al[14] reported weakness, lethargy, and fatigue as the most common reasons for referring cancer patients to emergency departments of hospitals. Barbera et al[15] concluded that fatigue was the most common reason for referring patients, nausea had the minimum prevalence, and the majority of patients were complaining about pain and dyspnea. With regards to the geographical differences in the field of cancer[16,17], it might be due to the geographical and epidemiologic differences in types of the cancers and the possible solutions applied in treating cancers in both countries. Haiderali et al[18] in America showed that nausea and vomiting were the most symptoms. However, Girmenia et al[19] concluded that most of the patients referred fever. In the study of Diaz-Couselo et al[20], fever, pain, and dyspnea were the most common causes for referring patients to Emergency Departments. Geraci et al[21] considered dyspnea the most common cause for referral of patients. Based on the clinical manifestations: fever was seen most in leukemia and lymphoma; ascites was seen most in colon, pancreas, and breast cancers; nausea and vomiting were seen most in breast, gastric, colon and pancreas cancers; constipation was only seen in colon cancer; loss of appetite was seen most in gastric and esophagus cancers; pain was seen most in colon cancer and multiple myeloma; dyspnea was seen most in lung and breast cancers; lethargy was seen most in gastric and colon cancers. Anemia, neutropenia, and leukopenia were seen most in colon cancer, lymphoma, and leukemia, respectively. It seems that the results are in proportion to the type of visceral involvement. For instance, constipation in colon cancer, loss of appetite in gastric and esophageal cancer, dyspnea in lung and breast cancer, were quite predictable, which confirms that it is possible to make appropriate plans to prevent developing the symptoms in patients and train them to take appropriate measures when confronted with such predictable problems. In this study, the maximum site of metastasis in patients was observed in liver, brain, and bone. There were significant relations between clinical manifestations and different types of metastases, as fever, ascites, nausea, vomiting, constipation, weakness and lethargy in patients with liver metastasis; pain and loss of appetite in patients with bone metastasis; dyspnea in patients with liver metastasis. In addition to the involvement

of major organs, patients with metastasis may suffer from the involvement of other organs such as lung, bone, liver, etc. Therefore, they are more prone to the risk of the complications caused by cancer as compared with other patients; it seems they refer to Emergency Departments more frequently and need further attention. As far as gender was concerned, loss of appetite in males and pain in females were seen most in this research. There were no differences between males and females as far as other symptoms were concerned; however, weakness and lethargy were rather higher in males. The higher rate of pain in the females might have been due to their more frequent referral to the Emergency Department. Males were able to endure pain further and they referred due to weakness, lethargy, loss of appetite, and consequently decreased ability to perform daily activities. Leukopenia and anemia exceeded significantly in males, which might lead to weakness and lethargy. Therefore, the high rate of this variable in cancer males should be taken into consideration. This might be due to the high rate of the cancers causing anemia in males or less attention of males to control anemia. In this research, anemia was found significantly in older individuals and neutropenia was found in young individuals.

CONCLUSIONS

The most clinical manifestations in the patients included pain, nausea, weakness and lethargy, and loss of appetite. Employing preventive methods and providing patients with required training may be useful in alleviating onset of nausea and vomiting in patients, reducing the frequency of referral of patients to the Emergency Department, and lowering financial burden of treatment costs of patients. There was a significant relation between the clinical manifestations and different types of metastases. In addition to the involvement of major organs, patients with metastasis may suffer from the involvement of other organs such as lung, bone, liver, etc. Therefore, they are more prone to the risk of the complications caused by cancer as compared with other patients; it seems they refer to Emergency Departments more frequently and need further attention. Anemia in males was exceeded in comparison to females, which needs further special attention, as it is closely related to prognosis and survival of cancer patients.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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