Original Article

Dengue Infection In Cancer Patients

Naveed Rashid, Faisal Sultan, Syed Hammad Nazeer, Aun Raza and Amjad Mahboob

Objective: To study the clinical behaviour of dengue infection in cancer patients.
Material and Methods: We reviewed medical records of cancer patients who were diagnosed with dengue infection in year 2011 as per discharge notes. Patients fulfilling revised dengue WHO/TDR classification with positive dengue IgM serologies were finally chosen for analysis.
Results: From initially screened 63 patients, 43 fulfilled revised dengue WHO/TDR classification criteria, 31 (of these 43) with positive dengue IgM were finally analysed. There were 16 males and 15 females, mean age was 39.0 (23.0) years. 23 patients were ≥ 18 years of age. 81% patients reported within first three days of illness. Major cancer bulk was from solid organ cancer group (n=21) followed by haematological group (n=10). Presenting features were fever (100%) followed by aches (58.1%), haemorrhagic manifestations (35.5%), vomiting (29%) and diarrhoea (25.8%). Twelve (38.7%) patients developed severe dengue with one death making 3.2% crude mortality rate.
Conclusion: The spectrum of dengue infection severity in cancer patients seems to be different from general population. Clinically dengue was more severe with solid organ cancers as compared to hematologic cancers possibly highlighting the role of cellular mediated immunity. Other risk factors identified were relatively elder age and more co-morbid conditions.
Key words: Dengue, severe dengue, cancer, Pakistan.

Introduction

Over the last few decades, dengue infection has become a global threat and this may be attributable to increasing prevalence of dengue vector species favoured by different factors associated with gradual urbanization of societies.[1-5] A growing population at risk also reflects that an ever larger number of those with altered or depressed immunity will also develop dengue infection because of the interplay of different host factors and pathogen as an important determinant for different clinical manifestations of dengue infection.[6-8] As the data on various clinical manifestations of dengue infection in cancer patients is scarce and is limited to case series or case reports only therefore we decided to review the clinical and laboratory characteristics of dengue infection among cancer patients from a tertiary care hospital in Pakistan.[9,10]

Material and Methods

This descriptive and retrospective study was conducted in Shaukat Khanum Memorial Cancer Hospital & Research Centre. This tertiary care cancer hospital caters cancer patients of all ages coming from different areas of the country. The hospital's electronic medical records (EMR) were reviewed for all those cancer patients who had a discharge diagnosis of dengue infection (either suspected or proven) admitted from January 2011 till December 2011. We defined dengue infection (1) as per criteria given in the revised dengue classification by World Health Organization (WHO) / TDR (UNDP-World Bank-WHO special program for Research and Training in Tropical Diseases) group in 2009 11 plus (2) positive dengue IgM (immunoglobulin M) serology as measured by Calbiotech Dengue virus IgM ELISA kit. According to WHO / TDR group, dengue infection is classified according to the presence or absence of different set of clinical and laboratory parameters. These include any patient who live in / travel to dengue endemic area with fever and 2 of the following criteria (a) nausea or vomiting (b) rash (c) aches and pains (d) positive Tourniquet test (e) leukopenia and (f) any warning sign. Warning signs include (1) abdominal pain or tenderness (2) persistent vomiting (3) clinical fluid accumulation (4) mucosal bleed (5) lethargy, restlessness (6) liver enlargement >2 cm (7) increase in haematocrit concurrent with rapid decrease in platelet count. Patients fulfilling above criteria but not having warning signs are defined as non-severe dengue without warning signs (NSD-) while patient having warning signs as well are defined as non-severe dengue with warning signs (NSD+). Severe dengue (SD) infection is defined if a patient has evidence of

(1) severe plasma leakage i.e. shock, fluid accumulation with respiratory distress (2) severe bleeding (3) severe organ involvement e.g. AST or ALT ≥1000 U/L, impaired consciousness, heart and other organs.

Out of total 63 cases retrieved from hospital's EMR, 43 fulfilled the revised dengue WHO/TDR group classification criteria. 31 out of these 43 patients had positive dengue IgM serologies and were selected for further analysis. Remaining 12 patients were excluded due to missing or negative dengue IgM serologies (Figure 1). Dengue IgG (Immunoglobulin G) results were not considered in screening these cases since this test was not uniformly performed in all patients. Amongst other laboratory parameters, unfortunately, liver function tests (available for 18 out of 31 patients) and peripheral blood smear to detect concomitant malarial parasites (available for 23 out of 31 patients) were excluded because of missing values in selected cases. Neutropenia was defined as absolute neutrophil count of < 500 neutrophils per ml. These finally chosen 31 cases with positive IgM serology were reviewed in detail for different parameters like demographic profile, clinical and laboratory features, clinical management, complications, follow up and outcomes. IBM SPSS version 19 was used for statistical data entry and calculation. An exemption from hospital's Institutional Review Board was taken along with the waiver of informed consent.

Results

The study analysis showed that all cases with dengue infection presented over a span of three and a half months from 26th July, 2011 to 6th November, 2011 (Figure 2). The basic characteristics of all patients are presented in Table 1. Twelve (38.7%) patients had severe dengue and only one patient died constituting a crude mortality rate of 3.2%. The distribution of different cancer patients who developed dengue infection is given in Table 2. The frequencies of presenting symptoms and warning signs (as per WHO/TDR group classification criteria) in dengue infected cancer patients are given in Table 3. Important laboratory and some relevant management parameters are summarized in Table 4. The dengue infection related complications were seen in five patients with severe dengue (SD) i.e. hepatitis (n=2), pleural effusion (n=1), acute kidney injury (n=1) and pulmonary embolism (n=1).

A total of twenty five (80.6%) cancer patients had received chemotherapy within last 1 year. Out of these, 13 (42%) patients received chemotherapy within last two weeks and 5 (16.1%) of them

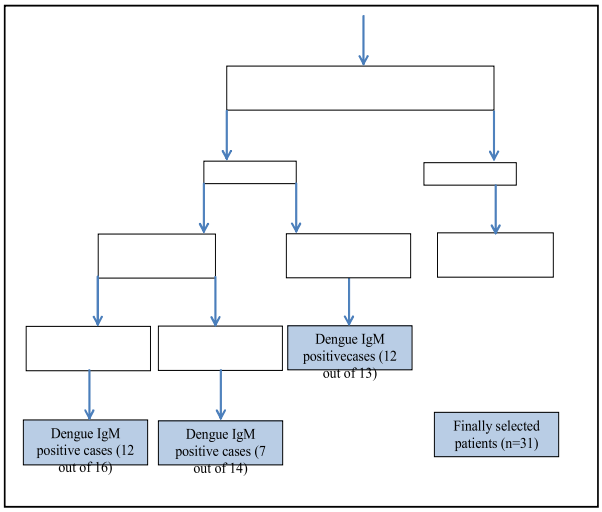

Fig-1: Flow chart of patients' selection schema. Hospital's electronic medical record was retrieved for cancer patients with the discharge diagnosis of dengue infection (n=63). Their data was reviewed according to dengue WHO / TDR classification. Those fulfilling the criteria (n=43) with positive dengue IgM serology (n=31) were finally chosen for the study.

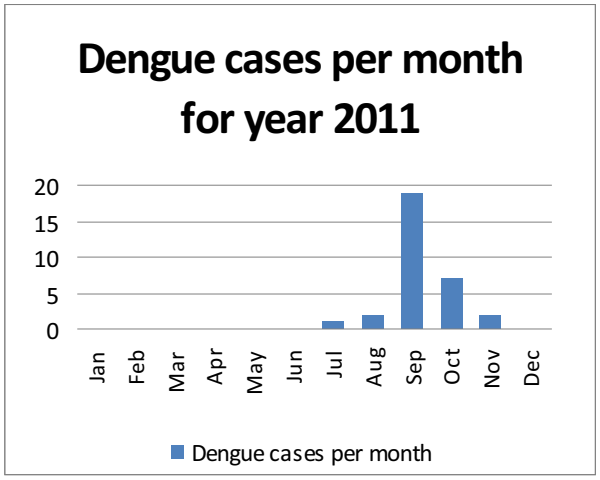

Fig-2: Distribution of dengue cases for year 2011. The maximum numbers of cases per month were seen in the post monsoon season (September and October 2011).

Table-1: Basic characteristics of dengue patients .

		Dengue Infection		
		Non Severe (n=19)	Severe (n=12)	Total (n=31)
Mean age (years)		36.0 (22.2)	43.7 (23.8)[a]	39.0 (22.8)
Age groups	<18 years	05	03	8
	> 18 years	14	09	23[b]
Gender distribution	Male	10	06	16
	Female	09	06	15
Days of illness at presentation	1-3 days	14	11	25[c]
	4-7 days	03	0	03
	> days	0	01	01
	Unsure	02	0	02
CO-morbidity	DM	0	03	03
	HTN	01	04	05
	IHD	0	01	01
	Dyslpidemia	0	01	01
	Hypothyroidism	01	0	01
	CLD	03	0	03

A=Mean age was higher in patients with severe dengue infection. b=Major bulk of patients was from adult age group (74%). c=Major p ortion of patients presented within 3 days of illness (81%).

Table-2: Basic characteristics of dengue patients .

Cancer Category	Cancers	Number of case
Solid organ cancers (n=21)	Breast cancer	05
	Nasopharyngeal cancer	01
	Laryngeal cancer	01
	Lung cancer	01
	Gastrointestinal stromal tumor	01
	Colonic cancer	01
	Rectal cancer	02
	Wilm's tumor	01
	Adrenal cancer	01
	Endometrial cencer	01
	Granulosa cell cancer	01
Hematologic cancers (n=10)	Acute lymphcytic leukemia	05
	Infantile leukemia	01
	Hodgkin's lymphoma	03
	Non-Hodgkin's lymphoma	01

Major bulk (68% cases) was from solid organ cancers while 32% cases were from hematologic cancers.

Table-3: Basic characteristics of dengue patients .

		Dengue Infection		
		Non Severe (n=10)	Severe (n=21)	Total n (%)
Symptoms	Fever	19	12	31 (100)
	Aches	12	6	81 (58.1)
	Mucosal bleed	3	8	11 (35.5)
	Nausea	2	2	4 (12.9)
	Vomitting	4	5	9 (29)
	Diarrhea	4	4	8 (25.8)
	Abdominal pain	03	3	6 (19.3)
	Cough	03	4	7 (22.6)
	Sore throat	02	3	5 (16.1)
	Dysuria	02	0	2 (6.4)
	Rash	02	0	2 (6.4)
Warning signs	Shock	0	4	4 (12.9)
	Altered mental status	0	5	5 (16.1)
	Lethargy/restlessness	1	8	9 (29)
	Respiratory distress	0	4	4 (12.9)
	Persistent vomtting	3	01	4 (12.9)
	Abdominal vomitting	3	7	10 (32.2)
	Pleural effusion	0	2	2 (6.4)
	Ascites	0	1	1 (3.2)
	Hepatomegaly	1	0	1 (3.2)
	Severe bleed	0	4	4 (12.9)

Table-4: Hematology and management parameters of dengue patients.

Hematology paramounts	Dengue Infection		
	Non Severe (n=19)	Severe (n=12)	Total (n=31)
High WBC (>11x10^3/ml)	0	2	2
Normal WBC (4-11x10^3/ml)	07	04	11
Low WBC (< 4x10^3/ml)	12	06	18
Percentage neutrophils (mean value)	53089%	58.98%	55.56%
Percentage lymphocytes (mean value)	30.80%	21.63%	27.25%
Normal HCT (≥35≤55)	12	05	17
Low HCT (<35)	07	07	14
High HCT (>55)	0	0	0
PLT mean value (10^3/ml)	100	142	116
Patients requiring platelet transfusions	06	08	14
Patients managed in outpatient / emergency	06	01	07
Patients needing admissions	13	11	24
Mean length of inpatient hospital stay (days)	5.9 (4.1)	9.7 (10.8)	7.7 (8.0)

WBC: White blood count, HCT: Hematocrit, PLT: Platelets

developed concomitant neutropenic fever. Only one of these five patients developed severe dengue infection. One another patient who did not receive chemotherapy also developed concomitant neutropenic fever with severe dengue. All patients with neutropenic fever recovered from dengue infection.

Discussion

Owing to scarce data in the form of case series or case reports of dengue infection in cancer patients and non-availability of any original article even as a descriptive study in the English literature that could specifically deal with the clinical and biochemical features of dengue infection in cancer patients we faced difficulty in building the discussion portion of study. Although direct comparison of our study with other studies is not possible due to above mentioned reason, where appropriate, we have mentioned the important findings from our purely cancer population focused study and same data from different local and international studies that mainly focus on general population group. We had almost equal gender distributions (**Table-1**) while other studies from Pakistan showed a male predominance. [12,13] We also had mixed population of both children and adult patients and almost three fourth (74.2%) of our patients were adult. This distribution is similar to the age pattern observed in a retrospective cross sectional study in Pakistan that extended over 5 years from 2003 till 2007. [13] Apart from the above mentioned reference most other studies in general population from regional countries have either been conducted on children or adults making estimate and comparison of distribution of dengue infection in different age groups difficult with reference to our study. [14,15] According to Ooi et al advancing age has a protective role in terms of morbidity up to a certain age limit and the likelihood of a dengue infection resulting in dengue haemorrhagic fever decreases when the infection shifts from childhood to young adulthood. [16] This effect, however, was not observed in our study where we found an almost equal proportion of severe dengue (SD) infection in adult (9/23) and non-adult cancer patients (3/8) but that could be attributed primarily to the difference in frequencies of different cancers in different age groups. This picture is further confounded by the fact that all cancer patients seen in this cancer hospital are not the true representative of the real distribution of different cancers with regard to different age categories in Pakistan yet this hospital caters the major burden of country's cancer patients. Another important finding was higher mean age of 43.7 (23.8) years in severe dengue (SD) group as compared to non-severe dengue (NSD) group i.e. 36.0 (22.2) years. This could have been partly due to the fact that our cancer patients' mean age of 39.0 (22.8) years was even higher than that observed in other regional and international studies. [13,14,17] Similarly a relatively greater number of comorbid conditions were seen in severe dengue (SD) group (29%) as compared to those in non-severe dengue (NSD) group i.e. 16% (**Table-1**). Whether these factors of higher mean age and comorbid conditions have a direct impact on prediction of dengue severity cannot be determined based on current study design but these can become good parameters for future studies.

The peak timing of the presentation and the distribution of cases in one calendar year in our study was similar to the recent trend of dengue fever in the region confirmed by a local study showing data from 2003 to 2007. [13] Most of the cancer patients (80.6%) reported within first three days of their illness. This finding probably is attributable to some extent to the relatively heightened awareness in recent years about dengue by media as well by the fact that cancer patients might be relatively more sensitized in their health seeking behaviour. [14]

Fever and body aches being the two major symptoms (**Table-3**) were seen in 100% and 58.1% cases relatively and these findings were also consistent with most other studies. [12,17,18,19] Similarly the risk of bleed in our study was seen more in adult patients (8 out of 11 patients with mucosal bleed and 4 out of 4 with severe bleed were adults) that was also observed by another large cohort on children and adults. [20] On the other hand we observed a relatively lower frequency of skin rash (6.5%) and vomiting (29%) in cancer patients (**Table-3**) as compared to the studies on general population. [12,18,20] The frequency of diarrhoea (25.8%) was relatively higher than reported by a study by Hammond SN et al. [19] Amongst laboratory parameters (**Table-4**), we found A clear association of different haematology parameters with the severity of dengue infection. Relatively severe leukopenia and thrombocytopenia was observed in non-severe dengue (NSD) group and was also observed in a study by Khan et al. [13] Moreover, in our study, the mean value of thrombocytopenia (30.13x10^9/L) in adults was lower as compared to that of non-adults (74.07x10^9/L). Similar finding was also observed by Trung et al. [20] We further noted relatively longer average length of hospital stay of our patients as

compared to the observations made by Trung et al. [20] We observed a broad spectrum of clinical presentations of dengue infection ranging from 38.7% of non- severe dengue without warning signs (NSD-) to 22.6% of non-severe dengue with warning signs (NSD+) and then to 38.7% with severe dengue (SD) infection (**Figure 1**) showing equal distribution of mild and severe cases on either end of the clinical spectrum. This distribution is different from the clinical spectrum observed in general population where relatively smaller fraction suffered from severe dengue (SD) and majority of patients had non-severe dengue with warning signs (NSD+). [21]

There are variable reports on the severity of dengue infection when compared with other immune-compromised groups possibly representing a different mechanism specific to each group. For example, according to a case series by Prasad et al, out of eight renal allograft recipients with dengue infection three patients developed haemorrhagic shock syndrome and died. [22] On the other hand dengue infection in HIV (Human Immunodeficiency Virus) patients was not reported to be associated with severe disease based on available small body of literature. According to a case report and a series of two HIV infected patients who acquired dengue infection had a benign course and their CD4 counts remained normal with no progression of HIV disease that might be indicating relatively little immune suppression. [23,24] Based on the fact that HIV infection weakens immune system by decreasing naïve and memory CD4 T lymphocytes and the fact that these cells are activated more in dengue haemorrhagic fever as compared to milder infections depict that possibly these interactions may be responsible for a fewer cases of dengue haemorrhagic fever in HIV co-infected patients. [25,26] Similarly in our study from the subgroup of haematological malignancies (n=10) with possible secondary defects in B and T cell functions only two patients (20%) developed severe dengue (SD) infection while from the subgroup of non-hematologic malignancies (n=21), severe dengue (SD) infection developed in ten patients (47.6%). The difference observed in dengue severity between the two subgroups might be related to the similar mechanism as is suggested in HIV patients with dengue infection above.

Neutropenic fever that was only seen in a small group of patients (n=6) where most of these (5 out of 6) also received chemotherapy further confounded the situation that whether it was purely chemotherapy or dengue virus related or the combination of both. Anyhow this finding played a protective role in the sense that all of these 6 patients have had full recovery. The authors think that the small size of neutropenic patients is the hindrance to draw any conclusion right now and will need further future studies for this association. Anyhow, by considering this finding along with the two another observations in the study i.e. (1) relatively more intense leukopenia in non-severe dengue (NSD) patients and (2) less severe disease in hematologic cancer patients highlights the pivotal role of immunity (especially cellular immunity) in the determination of severity of dengue infection that may be area of interest in further studies . The authors also suggest that other possible risk factors that may be taken into account for the future studies are the relation of primary cancer related immune depression, relatively elder age pattern and more comorbid conditions with the severity of dengue infection; the last two risk factors were seen more in severe dengue (SD) patients group (**Table 1**).

Although the only serological test available to prove dengue infection apart from clinical criteria at the time of study was dengue IgM serology and this also complies with the definition set by WHO / TDR group, yet, we could not differentiate between primary and secondary dengue infection because IgG serologies were not done in all patients. Furthermore, other confirmatory tests like NS1 (non-structural protein 1) antigen or dengue RT-PCR (reverse transcriptase polymerase chain reaction) were not available at the time of study. This study being purely descriptive with the lack of a control group (dengue fever in non-cancer patients) makes it difficult to know whether dengue is more severe in cancer patients or not.

To our knowledge so far there is no similar study published in the English literature thus this will be the first one with comprehensive description of clinical and laboratory behaviour of dengue infection amongst cancer patients from Pakistan. Based on some preliminary findings in the study suggesting possible role of cellular immunity in the determination of dengue infection severity will be a good variable to study in future research on this particular topic. Hence this study can work as a reference plate form in helping design future research work. Considering above limitations and strengths of the study, the authors suggest further future studies with a bigger sample size, well-designed format; choosing more homogenous cancer patients with complete clinical and laboratory follow up and the use

Of confirmatory tests for dengue infection. This would help in further elaboration of clinical and biochemical behaviour of dengue infection in cancer patients.

Conclusion

In conclusion, our study despite being a small sized descriptive one, that was carried out on cancer patients only, appears to have a different spectrum of dengue infection severities as compared to general population. Severe dengue infection was more common in patients with solid organ cancers compared with hematologic cancers, highlighting a possible role of cellular immunity in dengue severity determination. Those at risk of severe infection were also relatively elder and had more co-morbid conditions.

Department of Internal Medicine,
Rashid Latif Medical College, Lahore, Pakistan.

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