

Splenic Irradiation in the Treatment of Hypersplenism from Congestive Splenomegaly

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Abstract: Background: The aim of this study was to evaluate the efficacy of splenic irradiation in relieving symptoms and hematological disorders that accompanying hypersplenism from congestive splenomegaly in cirrhotic patients secondary to chronic viral hepatitis and if the presence of platelet-associated immunoglobulins (PAIGs) can affect the degree of thrombocytopenic recovery in these patients. **Patients, Methods:** Forty patients with hypersplenism from congestive splenomegaly subjected to splenic irradiation 20 Gy, 1 Gy / fraction biweekly using 3D conformal irradiation to protect surround structure. All patients were evaluated as regard clinical response, hematological parameters and splenic size before, during and after splenic irradiation. Quantitative assay of Platelet associated immunoglobulins (PAIGs) by flowcytometry was done before beginning of radiotherapy. **Results:** The radiation dose which used in this study induced a remarkable improvement as regard pain and thrombocytopenia, especially in cases with negative PAIGs, slight reduction of splenic size occurred. No considerable effect on anemia or leucopenia, there was no serious complications due to radiotherapy during treatment or follow up periods. **Conclusion:** Splenic irradiation could alleviate some symptoms and hematological disorders and that associate congestive hypersplenism in cirrhotic patients secondary to chronic viral hepatitis.

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1. Introduction

Pancytopenia in chronic liver disease can be due to hypersplenism, megaloblastic anaemia and primary bone marrow suppression. Hypersplenism is most common cause of pancytopenia in chronic liver disease. (1). Hypersplenism may occur as a primary disease or 2ry disease resulting from underlying disease or disorder (2). Hypersplenism is a clinical syndrome characterized by enlargement of spleen, reduction of at least one cell line in the blood in the presence of normal marrow function and evidence of increased release of premature cells such as reticulocytes or immature Platelets from the bone marrow into the blood. Hypersplenism is a treatable cause of pancytopenia. (1) Hypersplenism resulting from portal hypertension associated with congestive splenomegaly is frequently due to liver cirrhosis. The 5-year survival rate of untreated hypersplenism is only 50% and the usual treatment for hypersplenism is splenectomy or splenic embolization (3). However such modalities may be risky as they carry a high morbidity and mortality rate (4). Splenic irradiation is a non-invasive and alternative treatment for splenectomy and splenic embolization for patients with hypersplenism due to infiltrative diseases (5). Thrombocytopenia due to hypersplenism is usually a serious condition in

cirrhotic patients who have undergone invasive procedures (6).

Thrombocytopenia typically worsens with the progression of liver disease and can become a major clinical complication. Several mechanisms that contribute to thrombocytopenia have been proposed, including hypersplenism accompanied by increased platelet sequestration, platelet destruction mediated by platelet-associated immunoglobulins (PAIGs), and diminished platelet production stimulated by thrombopoietin (TPO). Serum TPO level may not be directly associated with thrombocytopenia in patients with chronic hepatitis and liver cirrhosis. In contrast, spleen volume and PAIGs are associated with thrombocytopenia in such patients, suggesting that hypersplenism and immune-mediated processes are predominant thrombocytopenic mechanisms (7).

Only few reports are available to evaluate the role of radiotherapy in management of hypersplenism from congestive splenomegaly (8).

The aim of this study was to evaluate the efficacy of splenic irradiation in relieving symptoms and hematological disorders that accompanying hypersplenism from congestive splenomegaly in cirrhotic patients secondary to chronic viral hepatitis and if the presence of platelet-associated immunoglobulins (PAIGs) can affect the degree of thrombocytopenic recovery in these patients.

2. Patients and Methods

Forty patients with hypersplenism due to congestive splenomegaly were referred to Clinical Oncology Department, Zagazig University Hospitals from July 2008 to August 2009. All patients were subjected to:-

- Thorough clinical examination,
- Abdominal ultrasound to evaluate the cases before starting treatment.
- Routine Laboratory investigations including:
 - Complete blood count (SYSMEX K1000).
 - Liver and Kidney function (ADVIA1650 Autoanalyzer)
 - B.M marrow Aspiration to exclude other causes of thrombocytopenia.
 - Detection of HCV Ab and HBsAg by using third generation ELISA technique.
 - Detection of HCV -RNA by using qualitative reverse transcriptase PCR (RT-PCR) by Roche

Diagnostics.

-Quantitative assay of PAIgs % by flowcytometry (FACS Calibur, Becton Dickinson,,SA) as follows: 3ml of venous blood were collected aseptically from each patient by veinipuncture into a sterile tube containing EDTA-2Na as anticoagulant. Platelet rich plasma was made by centrifugation(100 x g) for 15 min. the isolated platelets was washed twice by centrifugation (700xg)with 10 ml of phosphate buffer saline (PBS) containing 0.5%bovine albumin and 10 mM EDTA-2Na (PBS/EDTA) as 2.5 ml of PBS used for each time of wash. The suspension was adjusted to a platlet concentration of $50 \times 10^9/L$ ml of platelets. Fluorescein isothiocyanate (FITC)-conjugated F (ab)2 fragments of rabbit anti-human total Ig, IgG, IgM and IgA (Dako, Glostrup, Denmark) were used to detect PAIg. Pyroerythrin (PE)-conjugated CD41 monoclonal antibody (Becton-Dickinson, Franklin) was used to identify the platelet population. Platelets were dually stained with FITC conjugated antibody and PE-conjugated CD41 monoclonal antibody. Detection of PAIg by flow cytometry is an effective and highly specific method that quantify PAIg and determine the class of Ig (9).

Radiotherapy (RT):

Patients underwent CT simulation in a supine position for RT planning, with both arms raised above the head to facilitate use of lateral radiation ports. CT data were transferred to a 3D-CRT planning system (Precise). The spleen, liver, kidneys, stomach, and spinal cord contoured on each slice and reconstructed 3-D. The planning target volume (PTV) included a 1.5 to 2 cm margin around the spleen, An extra margin of 1 to 1.5 cm

was added in the craniocaudal direction to account for respiratory spleen motion and all patients were asked to perform shallow respiration to minimize this motion. RT planning aimed to minimize exposure of normal critical organs (normal liver tissue, spinal cord, stomach, etc.). RT was delivered using a linear accelerator (ELEKTA with 6 MV or 15 MV x-rays, depending on depth.

-Informed consent was obtained from the **patients.**

The patients were evaluated weekly during treatment and monthly thereafter for one year results were assessed by comparing physical findings, blood indices, abdominal ultrasound before and after radiotherapy to evaluate the response to splenic irradiation.

Statistical analysis

Data were entered, checked and analyzed using SPSS version 10.0 (Statistical Package for the Social science, Chicago, IL). Data were expressed as number and percentage for qualitative variables, and mean (X) \pm standard deviation (SD) for quantitative variables. paired "t" test and Chi-square (X^2) were used when indicated to assess significance $P < 0.05$ was considered significant.

3. Results

This study included forty patients, 25 males, 15 females, their ages ranged from 25 up to 66 years (mean 45 years). All patients gave history of liver cirrhosis. History of chronic hepatitis C presented in 65% of cases, chronic hepatitis B in 35% of cases, 60% of cases presented with mild to moderate degree of ascitis. Left upper abdominal pain was present in all cases but of variable degree. Epistaxis, bleeding gum, hemorrhoidal bleeding and ecchymosis, one or more of them were present in 80% of cases (**Table 1**).

As regard blood indices all patients presented with thrombocytopenia 65% had got platelets count less than $50 \times 10^3/cmm$ while the rest of patients 35% had got platelets count from 80×10^3 up to $100 \times 10^3/cmm$, hemoglobin was less than 10 gm / dl in 65% of cases while the rest of cases had more than 10 gm/dl, total leucocytic count was less than $3 \times 10^9/L$ in 40% of cases.

Follow up of cases during treatment period revealed improvement of upper abdominal pain as 60% of cases showed improvement of pain after the 7th sitting, 40% of cases showed pain improvement after the 10th sitting of radiotherapy. Pelvi-abdominal ultrasound after the 10th sitting of Rth showed reduction of splenic size 10-30% compared with pretreatment size and this reduction occurred in pretreated mildly enlarged spleen. Slight

improvement of platelets count without considerable improvement in WBCs or hemoglobin levels.

Post treatment follow up revealed that left upper abdominal pain as a subjective response relieved completely in 40% of cases where all cases of mild enlarged spleen showed complete pain relieve while cases with moderate and huge spleen enlargement showed lesser response as regard pain improvement (**Table 2**)

Cases of mild enlarged spleen showed 50% reduction of pretreatment size. Cases of moderate enlargement showed 50% size reduction in 40% of cases, and from 50% to 20% size reduction was found in 50% of cases and 10% of cases showed less than 20% reduction in size. As regard cases of huge splenomegaly no cases showed more than 50% size reduction while half of the cases showed less than 20% reduction in size and the other half gave less than 50% reduction in pretreatment size (**Table 3**). Positive platlet associated immunoglobulins was found in 65% of total cases - 70% of them has viral C hepatitis (**Table 4**).

Follow up of blood indices after treatment revealed that platelets count increase in all cases

(statistically significant $P < 0.001$) the mean value of improvement was 40% (range 1% to 60%) this improvement continued through the months of follow up period Leucopenia and anemia didn't show the same improvement ratio and some cases deteriorated (**Table 5**). Cases of leucopenia was managed medically without inetrruption of the treatment. Hemoglobin reaches less than 8 gm/dl in 12 cases (30%) which were managed with blood transfusion packed RBCs It was noticed that all cases of thrombocytopenia, which became more than $100 \times 10^9/L$ after irradiation was negative as regards PAIGs while all cases of thrombocytopenia which deteriorated or not increased above $100 \times 10^9/L$ was positive as regards PAIGs. In all cases of positive PAIGs the mean \pm SD of PAIGs was 71.2 ± 9.2 for total Ig, 58.3 ± 8.3 for IgG, 21.4 ± 2.1 for IgM, 23.5 ± 5.6 for IgA.

Epistaxis, gum bleeding, hemorrhoidal bleeding and ecchymosis improved in 90% of cases complaining of such symptoms before starting treatment.

No acute complications due to radiotherapy was found during treatment period or during the follow up period after splenic irradiation.

Table (1): Patients Characteristics.

Characteristics	NO	%
Age		
<50	26	65
≥ 50	14	35
Sex		
Male	25	62.5
Female	15	37.5
Abdominal pain		
Mild	10	25
Moderate	20	50
Severe	10	25
Spleen size		
Mild	12	30
Moderate	20	50
Huge	8	20
Child –pugh classification		
A	24	60
B	16	40
Hepatitis virus type		
B	14	35
C	26	65

Table (2): Pain evaluation pre and post treatment.

Pain severity	Pre-treatment		Post-treatment	
	No.	%	No.	%
No pain	-	-	16	40
Mild	10	25	10	25
Moderate	20	50	9	22.5
severe	10	25	5	12.5

Table (3): Degree of splenic size reduction after treatment

Splenic size reduction	Huge 8 (20%)		Moderate 20 (50%)		Mild 12 (30%)	
	No.	%	No.	%	No.	%
20 %	4	50 %	2	10%	-	-
20 – 50 %	4	50 %	10	50%	-	-
> 50%	-	-	8	40%	12	100 %

Table (4): Prevalence of platelet associated immunoglobulin (PAIg) in patients

	Platelet associated Ig			
	Negative		Positive	
	No.	%	No.	%
HCV 26	8	30.8	18	69.2
HBV 14	6	42.9	8	57.1
Total 40	14		26	

$$X^2 = 3.5 (P < 0.05)$$

Table (5): Blood indices before and after radiotherapy

Blood indices	Before treatment	After treatment	P
Hemoglobin (g/dl)	10.3 ± 1.2	10.8 ± 1.4	>0.05
WBCs ($\times 10^9/l$)	4.36 ± 2.3	4.65 ± 2.01	>0.05
Platelets Count ($\times 10^9/l$)	76.8 ± 23.5	93.5 ± 16.1	<0.001

* All parameters are expressed as $X \pm SD$

4. Discussion

Hypersplenism represents the increased pooling and / or destruction of the corpuscular elements of the blood by the enlarged spleen(10). Liver cirrhosis or portal hypertension is frequently associated with congestive splenomegaly resulting in hypersplenism (11). We focused our study on hypersplenism from congestive splenomegaly due to liver cirrhosis. Thrombocytopenia and leucopenia are probably the most common hematological disorders due to hypersplenism from congestive splenomegaly resulting from liver cirrhosis.(12). Peck-Radosavljevic's observed that, 15-70% of patients with liver cirrhosis have got thrombocytopenia, most commonly due to pooling of platelets in the enlarged spleen induced by portal hypertension(10). Thrombocytopenia in patients with liver cirrhosis has been reported to be caused by an increased platelet pool in the enlarged spleen (13), impaired platelet production in the bone marrow (14), decreased platelet function(15), and abnormalities in the platelet membranes(16). An article(17) reported that decreased production of thrombopoietin (TPO) might also promote the development of thrombocytopenia in liver cirrhosis. But TPO level may not be directly associated with thrombocytopenia in patients with chronic hepatitis and liver cirrhosis. In contrast, spleen volume and PAIgG are associated with thrombocytopenia in such patients, suggesting that

hypersplenism and immune-mediated processes are predominant thrombocytopenic mechanisms (7). Autoimmune mechanism plays an important role in the HCV-associated thrombocytopenia and spleen is a major source of PAIGs (1) So, autoimmune mechanism mediated by PAIg may play an important role in thrombocytopenia associated with chronic liver diseases (18).

In addition to thrombocytopenia anemia and Leucopenia are constitutes a common clinical signs of hypersplenism(19).

Hypersplenism can be treated with splenectomy or splenic embolization (4), but splenectomy in patients with huge splenomegaly and hematological disorders results in an uncommon high morbidity and mortality rate due to technical challenges and problems of hemostasis(20).

Thrombocytopenia which associates hypersplenism has been accompanied with an increased risk of bleeding when undergoing major surgery(8).

Splenectomy, could be associated with peri-operative complications such as post-splenectomy sepsis and a mortality rate as high as 14% (21)

Splenic embolization is an option for treatment of hypersplenism however splenic embolization may cause side effects, such as bacterial peritonitis, splenic abscess and acute or chronic liver failure, patients with uncompensated cirrhosis (19). Tarazov's study reported a high

mortality rate of 18% after splenic artery embolization for hypersplenism from liver cirrhosis.

Splenic irradiation is a non-invasive treatment option in managing hypersplenism (5).

Studies with chromium – 51 indicate that there is decreased red cell breakdown and increased red cell survival following splenic irradiation for chronic leukemia (22).

In our study, all patients showed improvement in thrombocytopenia during follow up period after splenic irradiation with a range (2% - 70%) (mean 36%) this improvement manifested clinically as an improvement in bleeding and ecchymosis in 90% of cases. It was noticed that cases with positive antiplatelet antibody showed lower degree of platelet count improvement after treatment. In contrast RBC'S and WBC'S didn't return to normal range which may be explained by the myelosuppressive activity of hepatitis viruses, and bleeding which associate liver diseases(5).

As regard splenic size only 10% of cases showed > 60% reduction of pretreatment size and 60% of cases showed 20% reduction of pretreatment size. Complete relief of pain was observed in 62.5% of cases. No acute complications (skin reaction, nephritis and enteritis) due to radiotherapy was found during treatment period or during the follow up period after splenic radiation.

Our results in this study coincide with the results reported by Mu, *et al.* who treated 5 patients with congestive hypersplenism with splenic irradiation, with a mean increase of 31% in platelet count with no considerable change in other hematological parameter. They reported reduction of splenic size in two patients and splenic pain improved in all patients (23).

Kenawi, *et al.*,(4) performed a study on 8 patients with congestive hypersplenism where they treated them with splenic irradiation daily up to 20 Gy, they observed no correlation between response and change in splenic size, with relief of splenic pain in all patients with variable degree,two of eight patients achieved a complete hematological response while three showed partial response.

Comparing the results of our study and the available results treating congestive hypersplenism with radiotherapy, it seems that splenic irradiation considered to be effective for thrombocytopenias, splenomegaly and splenic pain associated with hypersplenism from congestive splenomegaly. This approach is non-invasive and may be alternative for splenectomy and splenic embolization for cases with hypersplenism due to congestive splenomegaly. Pretreatment assay of PAIGs can

detect the immunological mechanism of thrombocytopenia in hypersplenism and give picture about response to irradiation therapy as negative PAIGs cases induced a remarkable improvement of thrombocytopenia after irradiation.

Further studies with a larger number of cases, may be with alteration of treatment schedules, as regard fraction size, total dose of radiation with longer follow up period are needed for better definition of the optimal and most effective dose of splenic irradiation which is needed for management of hypersplenism due to congestive splenomegaly.

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References:

- (1) Ashraf S. and Naeem S., 2010: Frequency of Hypersplenism in chronic liver disease patients presenting with pancytopenia. *Especial Eision Annals* Jan.-Mar. Vol. 16. No.1: 108 – 110.
- (2) Ferri ff. and Ferri's, 2007: *clinical advisor 2007: Instant Diagnosis and treatment*, 9th Philadelphia, Pa: Mosby,: 443.
- (3) Pursnani KG., Sillin LF. and Kaplan DS.,1997: Effect of transjugular intrahepatic porto systemic shunt on secondary hypersplenism – *Am J Surg.*; 173 (3): 169 – 173.
- (4) Kenawi MM., EL Ghamrawi KA., Mohammad AA., Kenawi A. and El-Sadek AZ., (1997): Splenic irradiation for treatment of hypersplenism from congestive splenomegaly. *Br J Surg*; 84: 860 – 861.
- (5) Nelson EW., Mon MC, 1999. Splenectomy in and high rish patients with splenomegaly. *AM J Surg.*; 178: 581 – 586.
- (6) Zuchini R., Huang CH., Tsai HW., Huang SC., Lin CP., Chen CY., Lee GB. and Lin XZ., 2010: Electromagnetic Thermoablation to treat thrombocytopenia in cirrhotic and hypersplenic rates, *Journal of gastroenterology Hepatology.* 25(9): 1578-86.
- (7) Sanjo A. Satio J. Ohnishi A. Maruno J. Fukata M. Suzuki N., 2003: Role of elevated platlet-associated immunoglobulin G and hyperspleenism in thrombocytopenia of chronic liver diseases. *J.Gastroenterol.*: 18 (6): 638-44
- (8) Guiney MJ, Liew KH, Quong GG, Cooper IA., 1989. A study of splenic irradiation in chronic lymphocytic leukemia. *Int J Radiat Oncol Biol Phy.*; 16: 225 – 229.
- (9)Nishioka T, Yamane T, Takubo T, Ohta,K, Park K And Hino M., 2005: Detection of various

- platelet associated immunoglobulins by flow cytometry in idiopathic thrombocytopenic purpura. *Clinical Cytometry*; 68B:37-42.
- (10) Peck – Radosavljevic M., 2001: Hypersplenism. *Eur J Gastroenterol Hepatol.*; 13: 317 – 323.
- (11) Nezman A, John M, Robert B. and Ira J., 2008: Thrombocytopenia associated with chronic liver disease. *Journal of hepatology*,48(6): 1000-1007.
- (12) Henry PH, Longo DL., 2001:Enlargement of lymph nodes and spleen. In *Harrison's Principle of Internal Medicine*. 15th edition New York: Mc Graw Hill;: 360 – 365.
- (13) Coons JC, Barcelona RA, Freedy T, Hagerty MF., 2005: Eptifibatide-associated acute profound thrombocytopenia. *Ann Pharmacother* ; 39: 368-372
- (14) Khaykin Y, Paradiso-Hardy FL, Madan M., 2003:acute thrombocytopenia associated with eptifibatide therapy. *Can J Cardiol*: 19: 797-801.
- (15) Ziporen L., Li ZQ., Park KS., Sabnekar P., Liu WY., Arepally G., Shoenfeld Y., Kieber-Emmons T., Cines DB. and Poncz M., 1998: Defining an antigenic epitope on platelet factor 4 associated with heparin- induced thrombocytopenia. *Blood*:92:3250-3259.
- (16)Curtis BR., Swyers J., Divgi A., McFarl JG. and Aster RH., 2002.Thrombocytopenia after second exposure to abciximab is caused by antibodies that recognize abciximab-coated platelets. *Blood*; 99: 2054-2059.
- (17) Li Q., Sun SZ., Wang BE., Jia JD., Ma H., Wei YX., Cong YL. and Shen J. 2004: The relationship among the counts of platelet, thrombopoietin and spleen index in patients with liver cirrhosis. *Zhonghua Gan Zang Bing Za Zhi.* ; 12(4):210-212.
- (18) Jiang XH., Xie YT. and Tan DM., 2004: Platelet associated immunoglobulin in the pathogenesis of thrombocytopenia in patients with chronic liver disease *Zhong Nan Da Xue Bao Yi Xue Ban* 29: 566-8.
- (19) Bash FN., Teran JC. and Mullen KD., 2000: Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. *Am J Gastroenterol*; 95: 2936 – 2939.
- (20) Hiatt JR., Gomes AS. and Machleder HI., 1990. Massive Splenomegaly. Superior results with combined endovascular and operative approach. *Arch Surg*; 125 (10): 1363 – 1367.
- (21) Sakai T., Shiraki K., Inoue H., Sugimoto K., Ohmori S., Murata K., Takase K. and Nakano T.,(2002):Complications of partial splenic embolization (PSE) in cirrhotic patients *Dig Dis Sci*; 47 (2): 388 – 391.
- (22) Awwad HK., Badeeb AD., Massoud GE.and Salah M., 1967. The effect of splenic x-irradiation on the ferrokinetics of chronic leukemia with a clinical study. *Blood*, 29: 242 – 256.
- (23) Liu MT., Hsieh CY., Chang TH., Lin JP. and Huang CC., (2004): Radiotherapy for hypersplenism from congestive splenomegaly. *Ann Saudi Med.*, 24 (3): 198 – 200.

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