

## Hepatitis C Positive Patients in Relation to Polyclonal and Monoclonal Gammopathy: An Egyptian Experience

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### Abstract

**Background:** Gammopathies is one of long term complication of chronic HCV Infection B-cell lymphoproliferative diseases produced by a clonal proliferation of plasma cells producing a unique immunoglobulin are known as monoclonal gammopathies. Their clinical spectrum includes monoclonal gammopathy of undetermined significance (MGUS) and overt multiple myeloma.

**Aim of Study:** The present study aimed to examine the prevalence, characteristics, and predictors of gammopathies in Egyptian patients with chronic HCV infection.

**Patients and Methods:** This study conducted a prospective cohort study on patients with bilateral baggy lower eyelids who underwent traditional lower blepharoplasty with fat excision or fat-sparing technique using the orbital septal plication method.

**Results:** The study was performed on 40 patients (20 patients per group). The right medial OGS showed a significant reduction in the fat-sparing and traditional groups ( $p < 0.001$ , each). However, the percentage of reduction was significantly higher in the fat-sparing group ( $35.8 \pm 2.8$  versus  $14.6 \pm 3.4$  in the traditional groups;  $p < 0.001$ ). Likewise, the left medial OGS showed a significant reduction in the fat-sparing and traditional groups ( $p < 0.001$ , each). The percentage of reduction was significantly higher in the fat-sparing group ( $35.9 \pm 2.9$  versus  $14.7 \pm 3.3$  in the traditional groups;  $p < 0.001$ ). Both left and right-sided central and lateral OGS showed a significant reduction in the fat-sparing and traditional groups ( $p < 0.001$ , each). However, the percentage of reduction was significantly higher in the fat-sparing group ( $p < 0.001$ , each).

**Conclusion:** In conclusion, the prevalence of polyclonal gammopathy was higher in patients with chronic HCV compared with monoclonal, which is reported to be related to old age. Patients with gammopathy were associated with anemia, altered coagulation profile, high alfa-fetoprotein, low albumin level, and leukocytosis. Enlarged spleen, male gender, WBCS  $< 5.000 \text{cc/mm}^3$ , and platelets below 120.000 are significant predictors of gammopathy in patients with chronic HCV.

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**Key Words:** Chronic HCV – Gammopathies – Egypt – Polyclonal gammopathy.

### Introduction

Extrahepatic symptoms are frequently linked with the clinical history of chronic hepatitis C virus (HCV) infection [1,2]. Essential mixed cryoglobulinemia (EMC) and lymphoma are two hematological complications of HCV infection [3,4]. EMC is the most prevalent extrahepatic manifestation of HCV infection, and it occurs more frequently in people who have had the virus for a long time [5]. Several investigations have found a relationship between lymphoma and HCV infection in both HCV-related type II EMC patients and individuals without EMC [6-8].

B-cell lymphoproliferative diseases produced by a clonal proliferation of plasma cells producing a unique immunoglobulin are known as monoclonal gammopathies [9]. Their clinical spectrum includes monoclonal gammopathy of undetermined significance (MGUS) and overt multiple myeloma. Smoldering and indolent myeloma are two different stages of myeloma [10]. Monoclonal gammopathies have no established cause; however, genetic predisposition and prolonged antigenic stimulation may contribute to their development [11,12]. Polyclonal gammopathy, on the other hand, is characterized by the broad activation of B cells and is linked to a variety of nonmalignant illnesses, including immune-related disorders and inflammation [13]. The likelihood of developing gammopathy increases with age, however, it is not common. In first-degree relatives, there is no risk of monoclonal gammopathies. This eliminates the necessity for screening siblings and children [14]. The most common symptoms of gammopathy are bleeding, increased bruising, recurrent infection, edema,

swelling, headache, pain, fatigue, and anemia. The issue of poly and monoclonal gammopathies among patients with chronic HCV is controversial and there seems to be some regional variation [15-17].

Therefore, the present study aimed to examine the prevalence, characteristics, and predictors of gammopathies in Egyptian patients with chronic HCV infection.

### Material and Methods

The current study gained ethical clearance from the Cairo University Hospitals and was planned per the recommendations of the STROBE guidelines [18]. We confirm that none of the study's procedures violated the main principles of the Declaration of Helsinki [19]. All patients signed the written informed consent before enrollment.

#### Study design and patients:

In this cross-sectional study, we recruited patients with chronic HCV from the outpatient clinics of the Hepatology Department, Cairo University Hospitals through the period from July 2014 to July 2015. We included adult patients (aged > 18 years old) with confirmed diagnosis of chronic HCV, with or without cirrhosis. Chronic HCV was defined as persistent positive anti-HCV or HCV RNA for more than six months. We excluded pediatric patients and HCV patients with confirmed cryoglobulinemia, autoimmune disease, malignancy, and/or positive human immunodeficiency virus (HIV) or hepatitis B virus (HBV) status.

#### Data collection and laboratory analysis:

All recruited patients were assessed, and the following data were collected: Age, gender, liver function tests, abdominal ultrasound (US), and electrophoresis testing findings. All patients underwent immunoglobulin electrophoresis, with a 2mL of venous blood withdrawn using a syringe. The blood samples underwent electrophoresis to separate the serum into serum albumin, alpha-1 globulins, alpha-2 globulins, beta globulins, and gamma globulins. The monoclonal and polyclonal gammopathies were identified in case of production spike-like and swell-like manners of immunoglobulins, respectively. Patients with suspected monoclonal and polyclonal gammopathies underwent gel electrophoresis to confirm the present of spike-like and swell-like manners of immunoglobulins, respectively.

#### Study's outcomes:

The primary outcome of the present study was to assess the prevalence monoclonal and polyclonal

gammopathies in patients with chronic HCV. The secondary outcome was to reveal the nature of gammopathy in patients with chronic HCV from Egypt.

#### Statistical analysis:

The statistical software MINITAB (16.0) was used for data processing and analysis. According to the normality of data distribution, the central tendency and variability of the numerical data were presented in the form of mean  $\pm$  standard deviations (SD) or median with interquartile range (IQR). Frequency counts and percentages summarized categorical variables. For testing of hypothesis, one sample test for proportions, (K.S) for two independent samples and Logistic Regression analysis (LR) were used. All previously mentioned tests were carried out using an  $\alpha=0.05$ .

### Results

The study was performed on 300 patients, with a mean age of  $48.1 \pm 13$  years old and male predominance (60.7%). The mean and standard deviation of the laboratory and imaging findings were estimated as shown in Table (1). The abdominal ultrasound shows abnormal finding in 182 (60.7%) cases. The spleen size was  $13.9 \pm 3$ . The spleen was enlarged up to 20% of its size in the affected patients.

Table (1): Characteristics of the studied groups.

Variables	Patients (N=300)
<i>Age (years):</i>	
Mean $\pm$ SD	48.1 $\pm$ 13
Range	18-85
<i>Sex (n, %):</i>	
Male	182 (60.7%)
Female	118 (39.3%)
<i>Laboratory findings:</i>	
HB	11.5 $\pm$ 2.1
WBCs	5.4 $\pm$ 2.5
Platelets	147.5 $\pm$ 80
Total bilirubin	2.2 $\pm$ 2.3
Direct bilirubin	1.4 $\pm$ 1.6
ALT	57 $\pm$ 23
AST	60 $\pm$ 26
Albumin	3.2 $\pm$ 0.9
PT	15.2 $\pm$ 4
INR	1.4 $\pm$ 0.3
AFP	8.6 $\pm$ 4.3
<i>U/S findings:</i>	
NAD	118 (39.3%)
Abnormal	182 (60.7%)
Spleen size (Mean $\pm$ SD)	13.9 $\pm$ 3

Overall, 57.7% (n=173) of cases had no gammopathy during electrophoresis testing. The rest of our result had (n=121; 40.3%) had positive polyclonal gammopathy while only six cases (2%) had monoclonal gammopathy (Fig. 1).

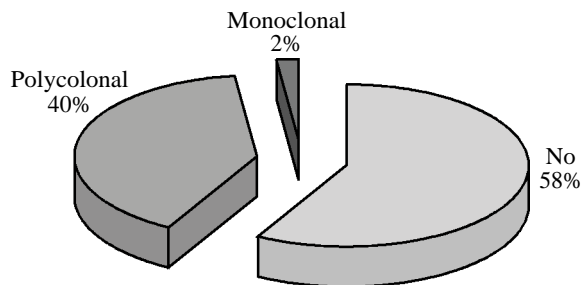


Fig. (1): Gammopathy in the study.

Concerning the association analysis there was a statistically significant association between presence of gammopathy and elderly ( $p=0.04$ ). While there was no difference between incidence of gammopathy in our group samples and gender. The analysis also showed that moderate low levels of hemoglobin, total leucocytic count, and platelets were highly significant in positive gammopathy groups ( $p<0.005$ ). Elevated bilirubin level and hypoalbuminemia were statistically significant in positive gammopathy group ( $p<0.05$ ). Indeed, neither ALT nor AST were associated with statistically significant correlation with incidence of gammopathy ( $p=0.67$  and  $0.23$ , respectively). By using one-sample t-test, coagulation profile markers (prolonged PT and higher INR) are associated with positive group gammopathy in higher statistically significant values ( $p=0.000$ ). Alpha fetoprotein and its significance in positive group of gammopathy was also tested with the last methods shows higher statistically significant value ( $p=0.005$ ).

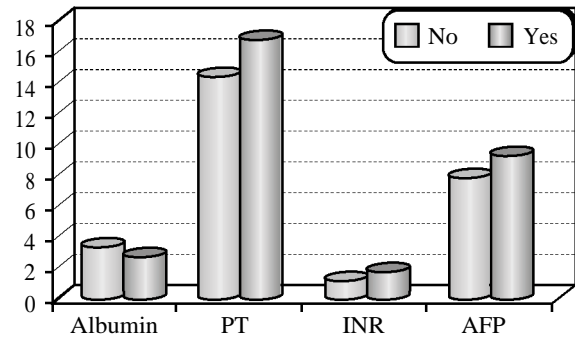


Fig. (3): Coagulation and liver biomarkers in positive and negative gammopathy.

There was statistically significant correlation between abnormal ultrasound findings and positive group gammopathy (83.5% of positive group gammopathy had enlarged spleen versus 16.5%). The spleen size was the most frequent finding associated with gammopathy group by using unpaired t-test. The mean and SD of size of spleen in positive gammopathy group is  $15.2\pm 3$  versus  $13.3\pm 3$  for negative gammopathy group.

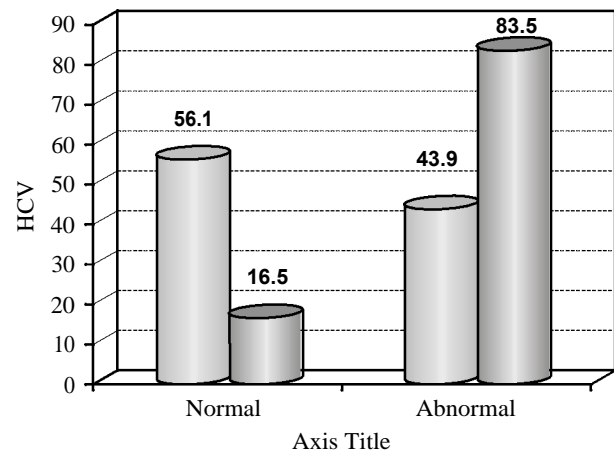


Fig. (4): US findings in positive and negative gammopathy.

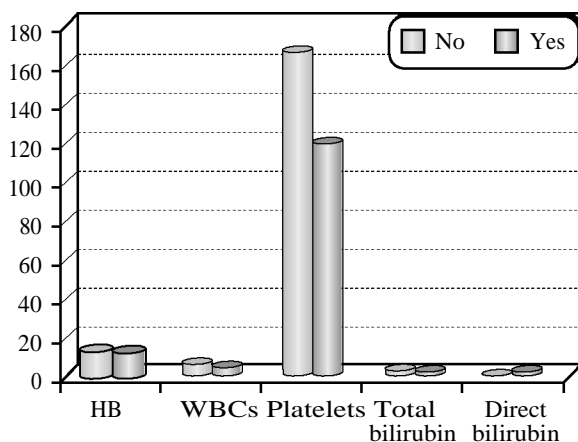


Fig. (2): Hematological and liver biomarkers in positive and negative gammopathy.

By using different parameters stated above, logistic regression analysis was done to delineate the predictors of gammopathy in patients with HCV disease. It has been found that enlarged spleen, male gender, WBCs  $<5.000\text{cc/mm}^3$  and platelets below 120.000 were considered predictors of gammopathy, Table (2).

Table (2): Relation between plasma protein electrophoresis versus different parameters by logistic regression.

Variables	Beta coefficient	p	Odd's (95% CI)
Abnormal sonar	0.18	0.000	1.7 (0.08-12.4)
Male	0.03	0.00	1.5 (1.2-6.5)
WBCs $<5$	0.19	0.02	1.1 (-0.1-11)
Platelets $<120$	0.02	0.04	1.09 (-0.02-13.7)

## Discussion

Lower In this perspective cross-sectional study, 40.3% of cases had positive polyclonal gammopathy and only 2% had monoclonal gammopathy. The prevalence of gammopathy was significantly ( $p < 0.05$ ) higher in older patients and male patients. Patients with gammopathy were associated with significantly ( $p < 0.05$ ) lower hemoglobin levels, total leucocytic count, and platelets. On the other hand, total and direct bilirubin levels were significantly higher in gammopathy patients compared to non-gammopathy patients. Similarly, Alpha-fetoprotein and coagulation profile markers, including PT and INR were significantly elevated in gammopathy patients ( $p = 0.005$  and  $p < 0.001$ ), respectively. Regarding the ultrasound, 83.5% of patients with positive gammopathy had enlarged spleen vs. 16.5% in the negative group, with a larger spleen size in the positive group. Logistic regression analysis showed a significant association between gammopathy and enlarged spleen ( $B = 0.18$ ,  $p < 0.001$ ), male gender ( $B = 0.03$ ,  $p < 0.01$ ), WBCS  $< 5.000 \text{ cc/mm}^3$  ( $B = 0.19$ ,  $p = 0.02$ ), and platelets below 120.000 ( $B = 0.02$ ,  $p = 0.04$ ).

The occurrence of poly and monoclonal gammopathies among HCV patients remains debatable. A monoclonal band was seen in 11% of HCV-positive patients in the study by Andreone et al., [16]; however, Mangia et al., found that the incidence of monoclonal gammopathies in patients with chronic HCV infection (17.9%) without cryoglobulinemia did not appear to differ from that of the general population (10%) [17]. In a Kuwaiti study, Al-Shemmari and his colleagues found that the prevalence of polyclonal gammopathies in chronic patients with HCV was 41%, and in patients who received interferon therapy, it was 31.8%. On the other hand, they could not identify any case of monoclonal gammopathy in this group of patients [15]. Similar to our findings, Tawfik et al., reported that the incidence of polyclonal and monoclonal gammopathies among Egyptian HCV patients was 40% and 2%, respectively [20], indicating that the polyclonal type is more common than monoclonal type in Egyptian patients with HCV. The low frequency of monoclonal gammopathies found in this study may be because monoclonal gammopathies are the disease of the elderly. In the general population, this disease affects roughly 1% of people between the ages of 25 and 65, and the majority of our patients are young. The lower frequency of MGUS in the normal population suggests an association of HCV infection with an increased risk for monoclonal gammopathy occurrence at an earlier age.

In the study of Caviglia et al., they investigated the prevalence and predictors of monoclonal gammopathy, B-cell non-Hodgkin lymphoma (B-NHL), and mixed cryoglobulinemia syndrome (MCS) in patients with chronic HCV. Their findings showed that monoclonal gammopathies were presented in 4.2% of the patients compared to 1.9% for MCS and 3.1% for B-NHL. In addition, they reported that cirrhosis was an independent predictor of the presence of monoclonal gammopathies in patients with chronic HCV (OR=2.89, 95% CI: 1.26-6.59;  $p = 0.012$ ). However, based on their findings, age ( $p = 0.933$ ), gender ( $p = 0.060$ ), and sustained virologic response ( $p = 0.688$ ) were not associated with monoclonal gammopathy. The same finding was observed with B-NHL and MCS [21].

Another study by Tanaka et al., reported that overall survival in patients with monoclonal gammopathy was significantly associated with four factors, including age, albumin level, hemoglobin level, and total protein. Patients with age less than 70 years old ( $p < 0.01$ ), albumin level  $> 3.5 \text{ g/dL}$  ( $p < 0.01$ ), hemoglobin level  $> 10 \text{ g/dL}$  ( $p = 0.03$ ), and total protein  $< 8.5 \text{ g/dL}$  ( $p = 0.03$ ) were associated with better prognosis and higher overall survival [22].

Bida and his colleagues investigated the associated diseases with monoclonal gammopathy. Their findings showed a non-significant association between monoclonal gammopathy with infections and parasitic disease, including chronic hepatitis, hepatitis C, sarcoidosis, and pulmonary tuberculosis. On the other hand, they observed a significant association between liver transplantation and monoclonal gammopathy (RR=5.9, 95% CI: 1.2-25.3;  $p = 0.03$ ), indicating that gammopathy was associated with the severity of the clinical condition [23].

This study has some limitations including the small sample size and the single-center setting of the study that may hinder the generalizability of our data. In addition, we could not assess the monoclonal gap and the survival analysis of patients due to the insufficiency of the data. Moreover, the implication of gammopathy on HCV condition in form of clinical severity and response to treatment was not assessed.

In conclusion, the prevalence of polyclonal gammopathy was higher in patients with chronic HCV compared with monoclonal, which is reported to be related to old age. Patients with gammopathy were associated with anemia, altered coagulation profile, high alfa-fetoprotein, low albumin level, and leukocytosis. Enlarged spleen, male gender,

WBCS  $<5.000\text{cc}/\text{mm}^3$ , and platelets below 120.000 are significant predictors of gammopathy in patients with chronic HCV.

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## العلاقة بين اضطراب متعدد النسيلة وآحادى النسيلة الغلوبيليني لمرضى الإلتهاب الكبدى الفيروسى نوع سى

تهدف الدراسة لمعرفة أوجه الترابط بين وجود اضطراب متعدد النسيلة واحادى النسيلة الغلوبيليني لمرضى الالتهاب الكبدى الفيروسى نوع سى فى عينة من المرضى المصريين.

هذه دراسة مسحية مسبقة تم اجرائها من الفترة يونيو ٢٠١٤ - يونيو ٢٠١٥ فى مستشفيات كلية طب القصر العينى وقد شملت ثلاثمائة مريض مصاب بالتهاب الكبد الفيروسى نوع سى جرى تعريضهم لسلسلة من الفحوصات السريرية والمناعية بالإضافة إلى التشخيص بالموجات الصوتية.

كانت نسبة المصابين بارتفاع معايير احادى النسيلة ومتعدد النسيلة الغلوبيليني هى ٢٪ و ٤٠٪ على التوالى فى دراستنا المسحية. أظهر عامل السن توزيعاً طبيعياً فى عينة البحث بمتوسط ٤٨.١ وانحراف معيارى قدره ١٣. تفاوتت أعمارالدراسة بين ١٨ إلى ٨٠ عاماً. فى حين كانت عينة البحث حاوية على نسبة ٢:١ رجال ونساء. أظهرت عينة البحث أثناء الفحص المناعى والفحص المختبرى سلسلة من المعلومات والنتائج التى ترتبط بحالة مريض التهاب الكبد المزمن منها انخفاض مستوى كريات الدم وانخفاض مستوى الصفائح الدموية مع حالة عامة من فقر الدم. اظهر فحص الموجات فوق الصوتية وجود تضخم فى الطحال بنسبة ٦٠ بالمئة من العينة مما يشير إلى ارتفاع تضخم الطحال بنسبة تفوق ٢٠ بالمئة من حجمه الأصى. أظهر البحث وجود ارتباط بعامل السن والجنس ونسبة الصفائح الدموية أقل من ١٥٠ الف صفيحة (ونسبة كريات الدم البيضاء) أقل من ٤ الاف كرية بالملم المكعب الواحد (لدى المصاب أن ظهور اضطراب الغلوبيلينية فى دراسات سابقة استفاضت فى الحديث عنه وعن علاقة هذا التحول فى إنتاج مجموعة من البروتينات من قبل خلايا البلازما فى نخاع العظم وعلاقته بأمراض مختلفة من جهة وكذلك علاقته بالتحول من حالة غير مستقرة انتقالية إلى تطور سرطانى مثل المايلوما المتعددة أو احدى أورام الغدد اللغفاوية من جهة أخرى. اختلفت هذه الدراسات فى تحديد نسبة التحول الغلوبيليني من ٠.٥٪ إلى ٦.١٪ من الجدير بالذكر ارتبطت عوامل وجود احادى أو متعدد النسيلة الغلوبيليني فى دراستنا مع الكثير من الدراسات السابقة ومنها عاملى السن والجنس مما قد يشير إلى سيطرة جينية أو سيطرة هرمونية ذكورية أو انتقاء من نوع معين يمنع حصول هذه التحولات السرطانية لدى النساء. نسبة تحول حالات اضطراب الغلوبيلينية إلى شكل سرطانى يساوى ١٪ سنوياً. لذلك انعقد لدى الباحث أهمية تشخيص ومتابعة الحالات التى يطرأ عليها نشاط مرتبط باضطراب الغلوبيليني لبروتين أم نتيجة تداخلها مع اضطرابات كثيرة ذات طبيعة سرطانية. لذلك فإن تشخيص اضطراب احادى أو متعدد النسيلة الغلوبيليني ذو أهمية للطبيب المعالج والمريض على حد سواء. هذا وقد اتفقت نتائج البحث مع نتائج البحوث العالمية مما يشير إلى عدم ارتباط الاضطراب الغلوبيليني بعلاقة اثنية بل بعلاقة مرتبطة بالجنس مما يحدو بالبحث مجدداً عن العلاقة ما بين الجنس من جهة والاضطراب الغلوبيليني من جهة أخرى.