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Original Article

Five years experience in kidney transplantation (TX) of HCV positive recepients in Egypt

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Abstract

The prevalence of HCV infection among chronic hemodialysis patients is around 85%. We present our follow up experience for 21 HCV antibodies +ve patients transplanted for more than 5 years. Liver biopsy was done to 10 of these cases but no single case has shown chronic active hepatitis. These patients were later found HCV RNA + ve by PCR. 20 HCV - ve Tx patients were included as control (C). All the 41 cases received their grafts from living donors. The two groups were matching in age, gender, etiology of renal disease, relation to donor, HLA matching, operative procedure and immunosuppression protocol (conventional triple therapy). Follow up plan was that used by our institute. Immunosuppression protocol did not change in either group except in four occasions in HCV + ve group and once in C group.

The 1st year survival of both patient and graft was 90.5% in HCV +ve group and 90% in C group (P>0.05 in either). Five years patient survival rate was 66.7% in HCV + ve group and 70% in C group (P>0.05), while graft survival was 66.7% vs 65% in the 2 groups respectively (P>0.05). Mortality was intimately related to liver cell failure in one case of either group while the 6 other mortalities of HCV + ve group were completely unrelated. Malignancy was reported in 3 cases of HCV + ve group but not in C group. Liver function tests were only mildly impaired in HCV +ve group in comparison to C group all through the five years of follow up.

Conclusion: The results of this prospective study should encourage transplantation teams to perform Tx to HCV +ve patients especially in Egypt in view of the very high prevalence of HCV viremia. The rationale of preoperative liver biopsy will be also discussed.

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Introduction

Hepatitis C virus appears to be responsible for 80% of post transfusion hepatitis, and up to 80% of sporadic hepatitis and cryptogenic cirrhosis [60]. Most patients depending on hemodialysis need transfusion of blood before kidney transplantation [4]. HCV infection is a common cause of liver disease in both patients undergoing organ transplantation and in the post-transplant period [64]. Testing for HCV RNA is important because some patients might not produce anti-HCV. Transaminase levels cannot be used as a surrogate marker of HCV infection in these patients [13]. The clinical implications of HCV infection in patients undergoing renal transplantation are unknown [60]. Anti-HCV in kidney transplant recipients increases the risk for the development of chronic hepatitis post-transplant. Anti-HCV is a significant risk factor for reduced kidney graft survival in blacks [21]. The presence of hepatitis C antibodies, before or after transplantation, is associated with a worse long-term survival rate for both the patient and the transplanted kidney in patients treated with quadriple therapy [23]. Although HCV appears not to cause aggressive liver disease in the early post transplant period, longer follow-up is needed to define the natural history of HCV in the renal transplant population [12,57]. The outcome of HCV infection after transplantation appears less severe than that of HBV infection: the survival of anti-HCV-positive patients is similar to that of anti-HCV-negative patients, at least during the first decade after transplantation. Liver biochemical abnormalities, serological markers and detection of HCV RNA are of little value to identify patients at greater risk of poor outcome after transplantation [25]. The presence of anti-HCV does not appear to alter long-term patient or graft survival, and histological evidence of severe chronic liver disease was rare in anti-HCV positive patients with chemical

hepatitis. From these results, the presence of anti-HCV antibody should not preclude kidney transplantation [47]. Significant, potentially life-threatening liver pathology manifests in about half of renal transplant recipients with chronic HCV infection. Liver histology correlates with the longitudinal biochemical profile. Patients with early onset of biochemical abnormalities and persistently deranged liver biochemistry are at risk of developing severe liver disease [14]. MPGN developed in five HCV-infected kidney recipients despite pharmacologic immunosuppression [56]. The recurrence of MPGN after transplantation in patients with chronic replicative HCV further elucidates the role of the viral infection in the pathogenesis of MPGN [11]. A clear association between HCV infection and the occurrence of type I MPGN in the allograft in renal transplantation was further confirmed. Terminal renal failure is the usual outcome [18,28]. However, HCV is preferentially associated with membranous glomerulonephritis (MGN) in renal transplant patients, rather than with membranoproliferative glomerulonephritis as in the normal adult population. MGN associated with HCV infection has a similar clinical picture and outcome to post transplant idiopathic de novo MGN, with persistent massive proteinuria and progressive deterioration of renal function [11,45]. Renal thrombotic microangiopathy associated with anticardiolipin antibodies was recently described in hepatitis C-positive renal allograft recipients [1]. Cryoglobulinemia was present in 32% of the HCV-positive hemodialysis patients, 5.9% of the HCV-negative hemodialysis patients, 37.8% of the HCV-positive kidney transplant recipients, and 27% of the HCV-negative kidney transplant recipients. Cryoprecipitate in 56.3% of the HCV-positive cryoglobulinemic hemodialysis patients and 53.8% of the HCV-positive cryoglobulinemic kidney transplant recipients contained HCV-RNA. Interestingly, the cryocrit values among hemodialysis and kidney transplant patients were much lower than these in other reports on nonrenal failure cases. Also, the cryoglobulinemic syndrome (with purpura, arthralgia, etc.) in hemodialysis and kidney transplant patients with cryoglobulinemia was not common [65]. Recipients with anti-HCV prior to transplantation have increased risk of post transplantation liver disease, graft loss and death [10,50,38]. Fibrosing cholestatic hepatitis and vanishing bile duct syndrome are early and severe complications after renal transplantation [9,20,62] which appears in patients with ongoing HCV infection under azathioprine therapy, despite a nonaggressive immunosuppressive protocol. Both HCV and azathioprine could play a concurrent role in the pathogenesis of this severe complication after renal transplantation [46]. On the other hand, Haem et al. concluded that HCV infection did not appear too deleterious for the liver in this cohort of patients [27]. HCV infection in patients under immunosuppressive therapy causes only a mild liver disease, as determined by clinicochemical and clinical parameters, and that mortality rate is not increased [26]. Although glomerular lesions and more severe infections can appear in hepatitis C virus patients, graft and patient survival rates in most series are similar to those in hepatitis-C-negative patients [44]. HCV-positive renal transplant recipients had a better survival than similar HCV-positive patients awaiting transplantation [36]. HCV infection at the time of referral for transplantation is associated with an increased risk of death, irrespective of whether patients remain on dialysis or undergo transplantation. Transplantation has a beneficial rather than adverse effect on long-term survival in anti-HCV positive patients. Hence, anti-HCV positive status alone is not a contraindication for renal transplantation [49]. Renal transplantation may not be associated with an increased risk of progressive liver disease in HCV-positive patients, compared with ESRD patients receiving chronic dialysis [24]. Using conventional immunosuppressive regimen, renal transplantation is associated with a more severe evolution of chronic hepatitis C as compared with HCV-infected immunocompetent subjects [68]. Pretransplant evaluation of both anti-HCV and HBsAg positive pts should include liver biopsy to exclude potential recipients with CAH [42,61].

Aim of work

The aim of this prospective study is to elucidate the prevalence of HCV infection among the potential candidates of kidney transplant in Egypt, namely the chronic hemodialysis patients, to study the hepatic pathology in these affected patients and to follow up HCV infected kidney transplant recipients looking for the short and long term consequences of this infection on their postoperative course.

Material and methods

We started this study by doing a survey to all patients treated by regular hemodialysis treatment in seven large governmental and private centers in Cairo. This survey included 263 cases. The test that was available by that time was ELISA 2nd generation. This prevalence varied from one center to another and ranged between 80% and 100% (figure 1).

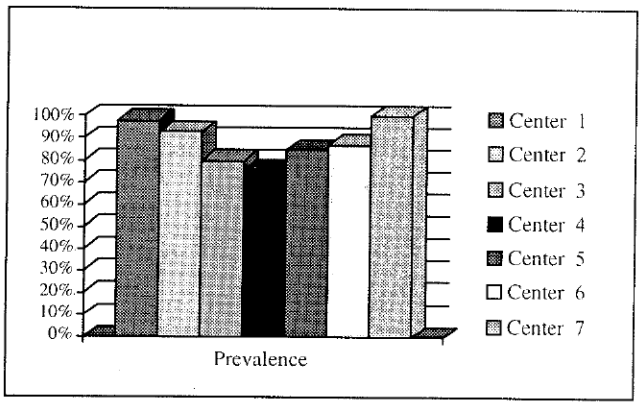

Fig. 1. Prevalence of HCV infection among chronic hemodialysis patients

The 2nd step was to perform percutaneous liver biopsy to all kidney transplantation candidates that proved to have HCV infection. Liver biopsy was done to 10 of these cases.

We then recruited all HCV +ve patients that performed kidney transplantation in our center during 1993 and 1994 (21 cases) in our follow up study. The 20 HCV -ve kidney transplant patients that performed the operation during the same period were included as control group.

All the 41 cases received their grafts from living donors (5 related versus 16 unrelated donors in HCV +ve group and 5 related versus 15 unrelated donors in HCV ve control group) [figure 3]. The two groups were matching in age, gender, etiology of renal disease, HLA matching, operative procedure and immunosuppression protocol.

The etiology of chronic renal failure in the 2 studied groups is shown in figure 2. The donors of most cases matched with their recipients in 3 loci, one of Dr, 1 A locus and 1 B locus and repeated -ve crossmatch was a must in all cases. The implanted graft was connected to the right internal iliac artery in 18 cases in either group, remaining cases had anastomosis to either the right external iliac or the left internal iliac arteries, the renal vein was always connected to the external iliac vein and antireflux uretrovesical anastomosis using a ureteric stent was done in all cases with the exception of 2 patients in either group (table 1).

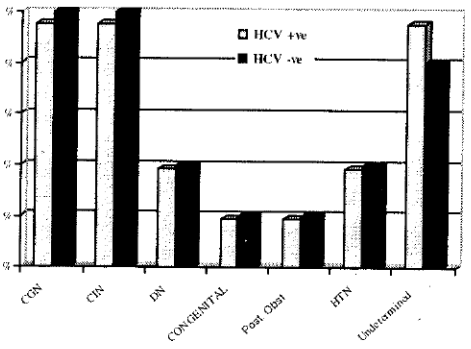

Fig. 2. Etiology of CRF in the 2 groups

Table 1. Preoperative and operative details in the 2 groups

	HCV+ve	*HCV-ve*	*P*
Age	42 ± 9.4	40.8 ± 11.1	N.S.
Male/female	14/7	14/6	N.S.
HLA mismatch			
1	3	2	
2	3	3	N.S.
3	14	15	
4	1	0	
Ischemia time	51 ± 7.6 min	49.5 ± 9.4	N.S.
Arterial Anast.	18/3	18/2	N.S.
Venous Anast.	Ext. Iliac	Ext. Iliac	N.S.
Ureteric Anast.	19/2	18/2	N.S.

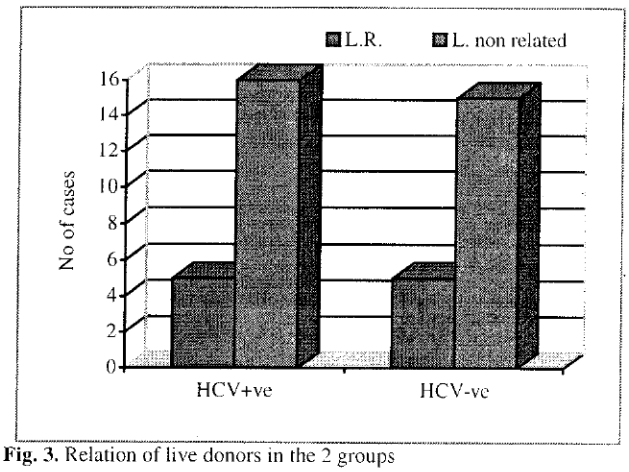

Fig. 3. Relation of live donors in the 2 groups

The immunosuppression protocol used in all cases consisted of azathioprine given as 1 mg/kg 48 hours before surgery (-48 hours), 2 mg/ kg given -24 hours, -6hours and daily thereafter, cyclosporine A given as 8mg/kg/ day as 2 equal doses starting -48 hours and dose is adjusted postoperative according to its whole blood trough level (level measured just before the intake of next dose) [figure 4], and prednisolone given preoperative as 3 IV doses of 250 mg each at -12 hours, anesthesia induction and just before declamping then the dose is gradually tapered post operative till a daily morning oral dose of 7.5 mg is reached by the end of the 1st postoperative year (figures 4,5).

The immunosuppression protocol did not change in either group except in four occasions in HCV +ve group and once in C group, azathioprine was discontinued in these cases due to hepatic toxicity. In 2 of these cases mycophenolate mofetil (MMF) was used instead of azathioprine as rescue therapy.

Follow up plan was that used by our institute, the postoperative hospital stay ranges between 10 and 14 days, following discharge the patient visits the outpatient clinic twice weekly in the 1st month after discharge, weekly in the following 3 months, every 2 weeks till the end of the 1st year and monthly thereafter. During each visit the patient undergoes thorough clinical examination including recording of vital signs, and then blood and urine samples are collected to do complete blood count, fasting blood sugar, serum cholesterol and triglycerides, serum urea, creatinine, uric acid, calcium, phosphorus, sodium, potassium and complete liver function tests including liver transaminases, alkaline phosphatase, bilirubin, serum albumin and prothrombin concentrations. Trough level of blood cyclosporine A was estimated twice monthly initially and once monthly thereafter. Urine analysis was done in every visit and 24 hours urine proteins were estimated every three months. All the results of every patient were kept in his own file after recording them in a cumulative sheet designed for this purpose.

The initial and final data were then statistically processed using IBM PC applying appropriate statistical methods i.e. Student t test, and simple linear correlations [7].

- Neoral 8mg/Kg in 2 divided doses starting -48 hours.
- Azathioprine 1mg / kg -48, 2mg / kg -24 and -6 hours.
- Methyl Prednisolone 250 mg -12 hours, with anesthesia induction and during declamping.
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Fig. 4. Induction immunosuppressive treatment

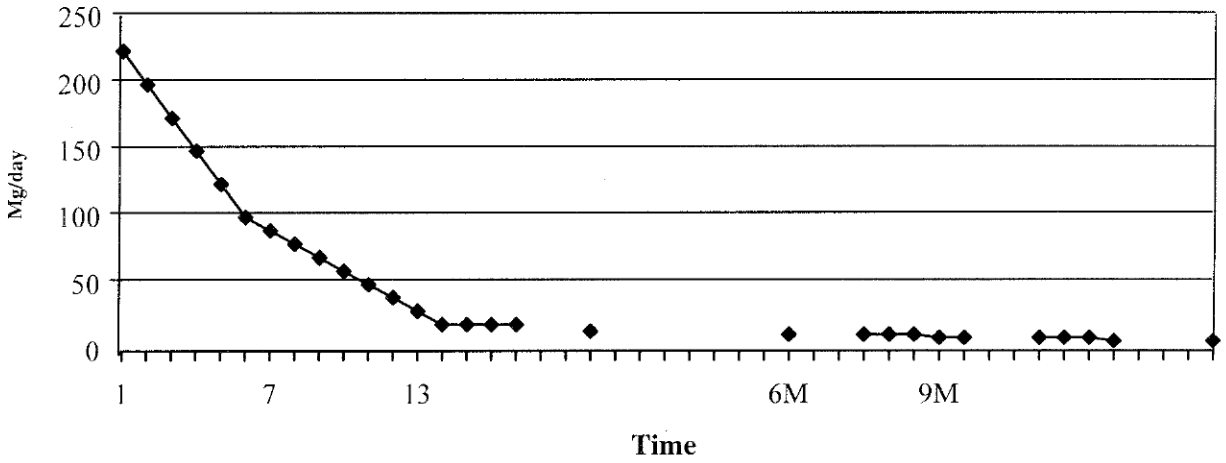

Fig. 5. Steroid dose tapering pattern

Cy. A trough level:

- 1st 3 months: 250 - 400 ng/ml
- 3 - 6 months: 150 - 250 ng/ml
- 6 - 12 months: 100 - 200 ng/ml
- Afterwards: 100 - 150 ng/ml

Fig. 6. Recommended CyA Blood level at different intervals after transplantation

Results

Results are shown in figures 7-16 and tables 2-3. The prevalence of HCV infection in the 7 centers studied is 85.4%. Figure 7 shows the results of liver biopsy in the 1st 10 HCV+ve cases recruited in this study. 4 cases showed large droplet fatty infiltration, 2 cases had chronic lobular hepatitis, 2 cases had chronic persistent hepatitis, one case had hydropic degeneration affecting hepatocytes and another one had evidence of schistosomal granulomatous infiltration but without any evidence of viral affection. No single case has shown any evidence of chronic aggressive hepatitis.

When polymerase chain reaction became available to detect HCV ribonucleic acid of the virus genome, we tested all the surviving cases and the test was +ve in all HCV +ve cases, confirming their affection by this virus.

The 1st year survival of patients infected with HCV was 90.5%, only 2 cases died during the 1st year of follow up. 2 cases in the control group also died during this year; hence the 1st year patient survival in this group is 90%. All surviving cases in both groups had functioning grafts by the end of this 1st year of follow up and hence the graft survival was 90.5% and 90% in both groups respectively (P>0.05 in either). Five years patient survival rate is 66.7% in HCV +ve group and 70% in C group (P>0.05), while graft survival is 66.7% vs 65% in the 2 groups respectively (P>0.05) [figure 8]. Mortality was intimately related to liver cell failure in one case of either group while the 6 other mortalities of HCV +ve group were completely unrelated (table 3).

There was no significant difference in either the serum creatinine or the encountered urine abnormalities in between the 2 groups studied (figure 15 and table 2).

Malignancy was reported in 3 cases of HCV +ve group but not in C group. The 1st case developed Kaposi sarcoma involving the scars of transplant surgery and the old AV fistula discovered during routine follow up 1.5 years after operation, The 2nd developed anemia and hypercalcemia and was diagnosed by serum immune-electrophoresis and bone marrow aspirate to have multiple myeloma by the 32nd month post-operative and the 3rd presented by a hard swelling in the left hypochondrium proved by ultrasonography and C.T. scan of the abdomen as heterogenous mass related to the body of the stomach and gastrosplenic ligament. C.T. guided biopsy and histopathologic examination proved a high-grade non-Hodgkin lymphoma, this event happened during the 43rd post-operative month (figure 16).

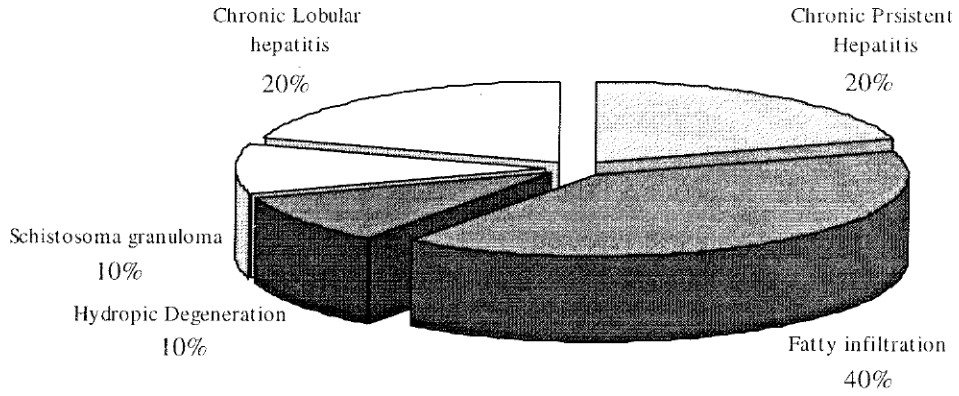

Fig. 7. Different histopathologic findings encountered in HCV +ve cases

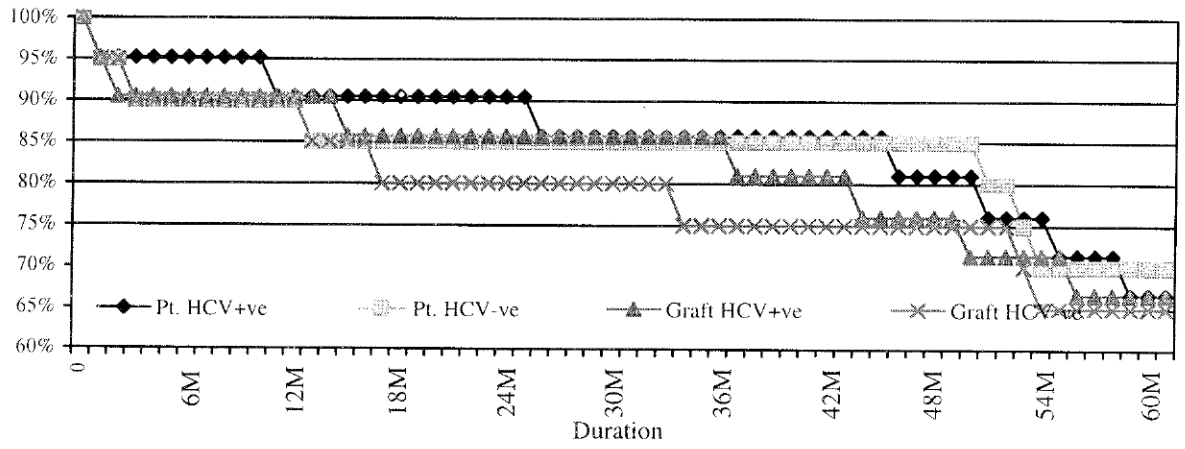

Fig. 8. Patient and graft survival curves in the 2 groups

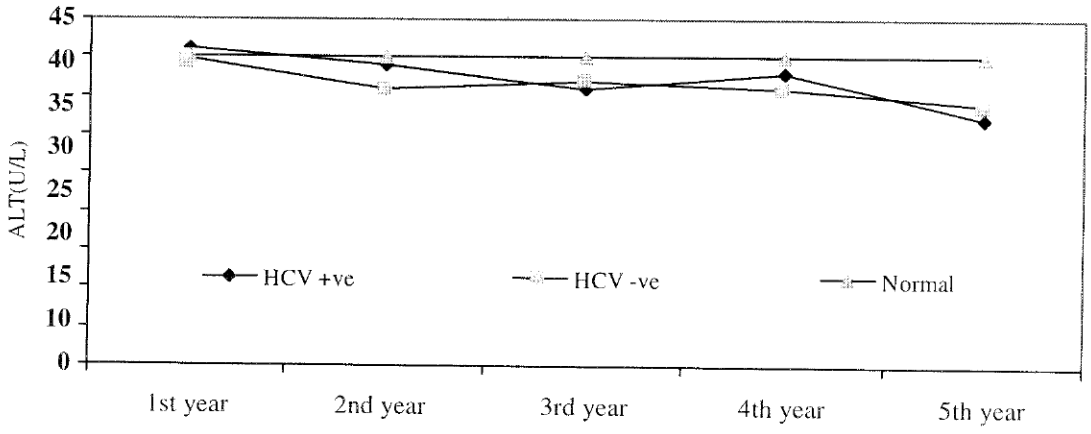

Fig. 9. Srum ALT in the 2 groups

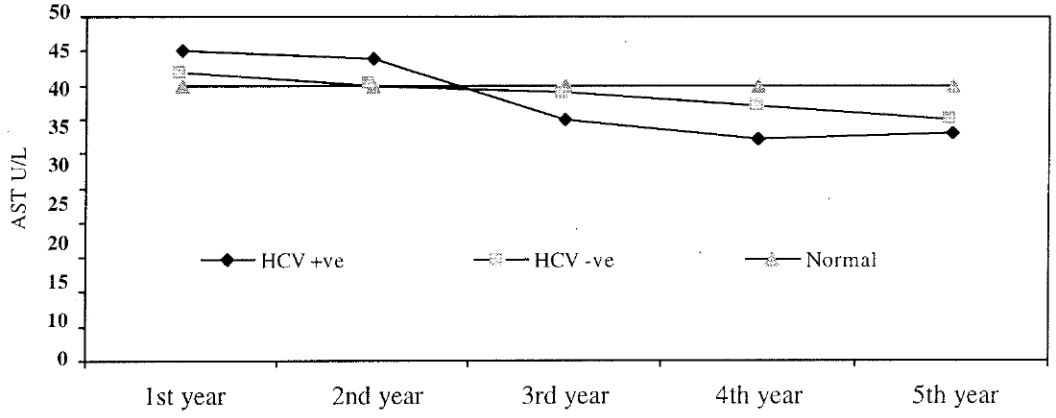

Fig 10. Serum AST in the 2 groups

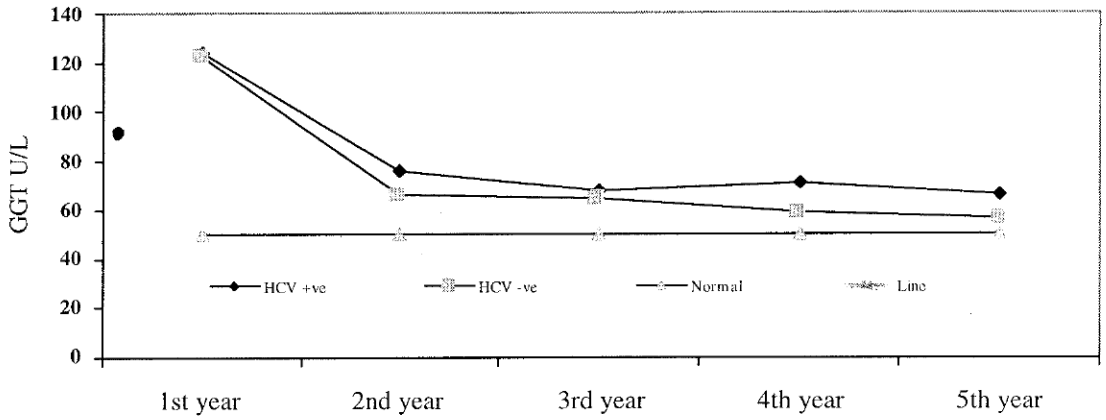

Fig. 11. Serum GGT in the 2 groups

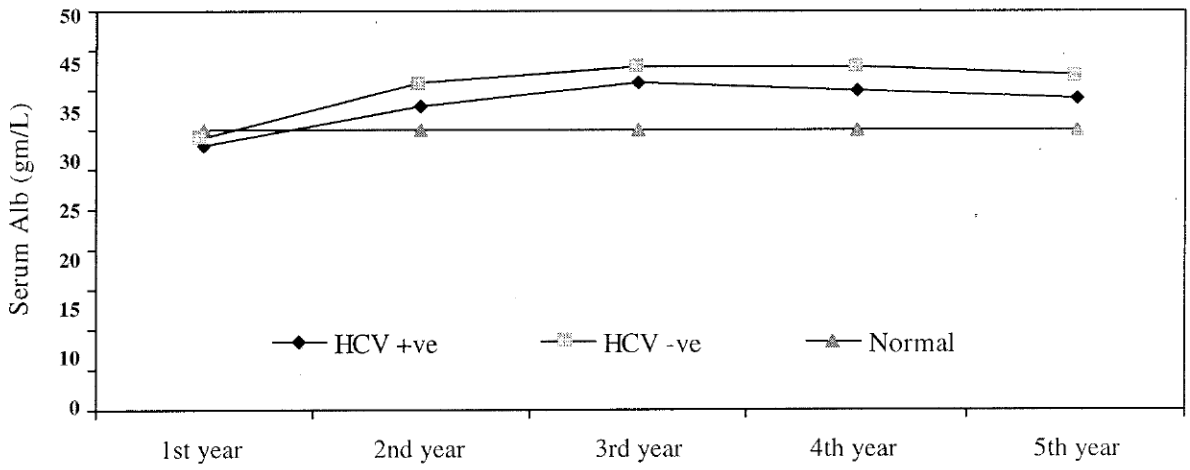

Fig. 12. Serum albumin in the 2 groups

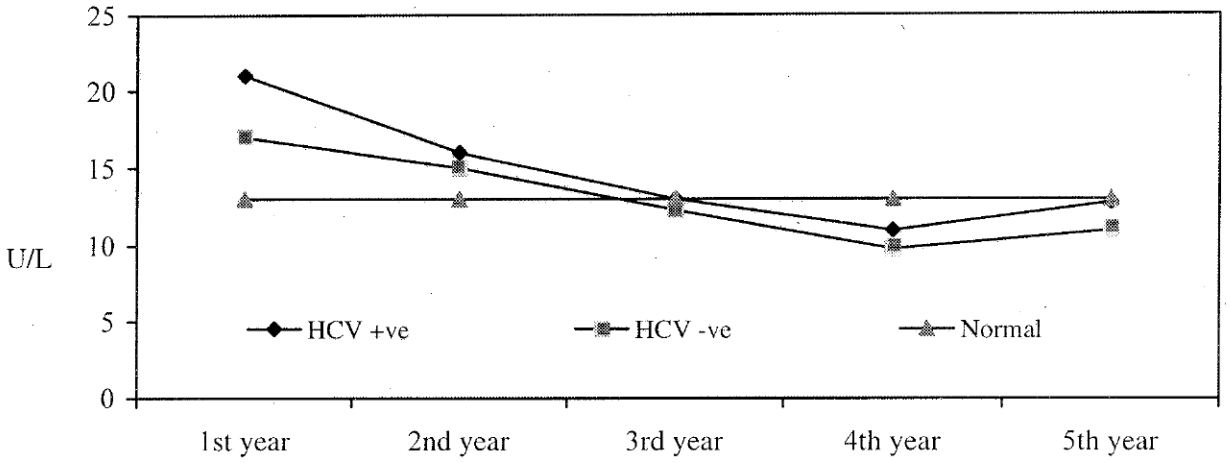

Fig. 13. Serum alkaline phosphatase in the 2 groups

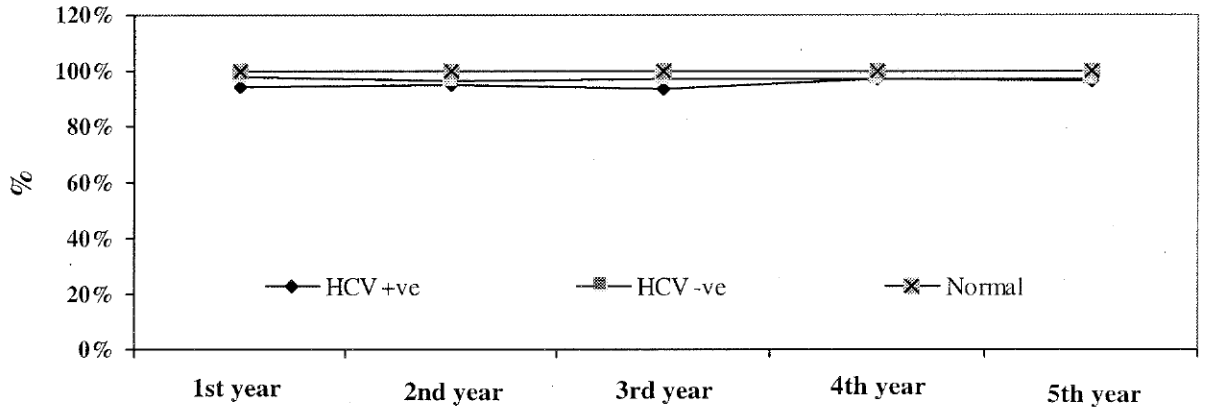

Fig. 14. Prothrombin concentration in the 2 groups

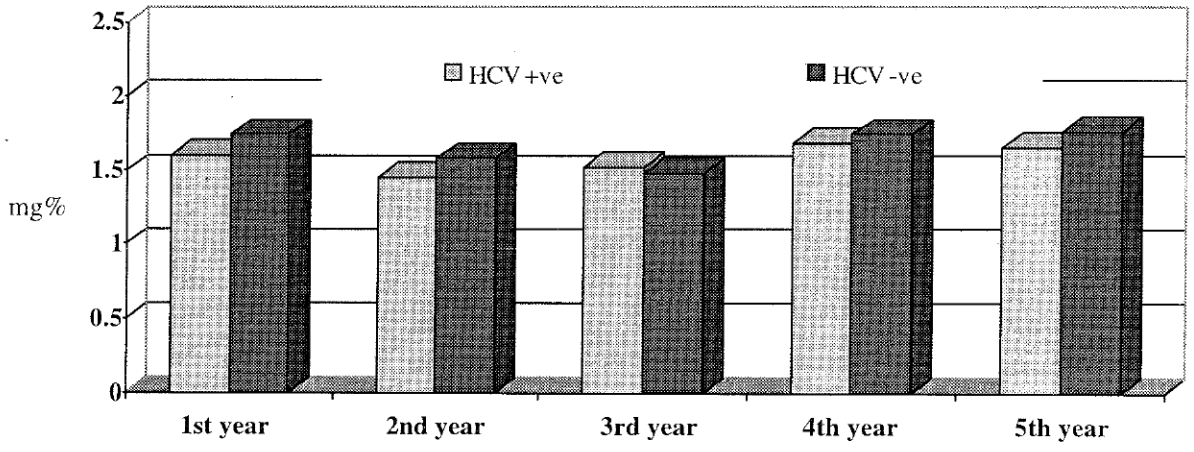

Fig. 15. Serum creatinine in the 2 groups

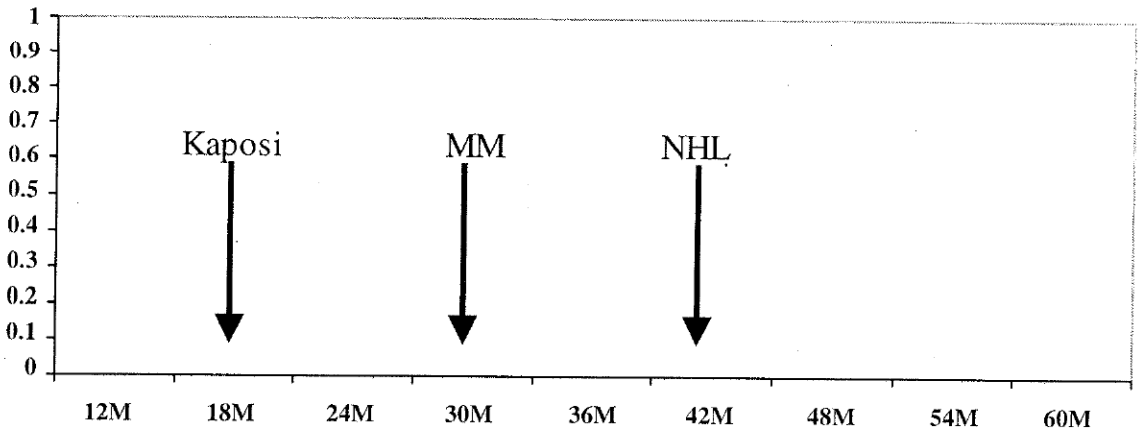

Fig. 16. Time of discovery of malignancy in the affected victims

Table 2. Urine findings in the 2 groups

	HCV +ve	*HCV -ve*	*P value*
24 hours protein	0.73 ± 0.36	0.69 ± 0.49	>0.05
WBCs (/HPF)	3.11 ± 2.69	3.18 ± 1.76	>0.05
RBCs (/HPF)	8.47 ± 5.19	7.23 ± 6.28	>0.05

Table 3. Causes of mortality in the 2 groups

Cause of Death	*HCV +ve*	*HCV -ve*
Sepsis	2	2
LCF	1	1
Cadiovascular	2	3
Malignancy	2	0

P>0.05

Although the level of alanine transaminase enzyme activity did not show any significant difference between the 2 studied groups all through the 5 years of follow up, serum aspartate transaminase enzyme activity tended to be higher during the 1st 2 years of follow up (P=0.058) and then became significantly lower during the 4th follow-up year. On the other hand, the serum gamma glutamyl transpeptidase enzyme activity was significantly higher in the 2 studied groups compared to the normal control of the lab during the 1st 3 years of follow-up but without appreciable difference in between the 2 groups studied. During the 1st year serum alkaline phosphatase enzyme activity was significantly higher in HCV+ve group compared to HCV-ve group and the normal lab control (P=0.05 and 0.038 respectively. Afterwards, this difference was no more encountered. On the other hand, there was no significant difference in either serum albumin level or the prothrombin concentration all through the 5 years of follow-up (figures 9 -14).

Discussion

Chronic hepatitis C viral infection is a common problem in renal allograft recipients [6]. The prevalence of this viral infection among chronic hemodialysis patients in Egypt is very high as evidenced by our initial survey to 7 dialysis units in Cairo. In Spain, where hepatitis C infection is more endemic than other western European countries, the prevalence of anti-HCV at transplant time was 48%, and was related to the time on dialysis and to the amount of blood transfusions. Transmission of this virus within the dialysis unit can happen if the universal precautions are not followed [5]. The presence of anti-HCV antibody after transplantation was determined by the patient status on dialysis, 80% of them being positive before surgery [41].

tion is an important cause of post transplant chronic hepatitis in HBsAg-negative patients [33]. Chronic HCV infection is usually associated with liver dysfunction and persistent infection is common [43]. Liver histological lesions are correlated with HCV viral replication, are more frequent in patients treated with azathioprine and are more severe as the duration of transplant is longer [31]. Post transplantation liver disease due to HCV is an important cause of morbidity and mortality in renal transplant recipients [3,10,23,29,38,42,48,50,54,59,66]. In addition, HCV patients have a high prevalence of severe acute pathologic findings in renal allograft biopsies obtained early after transplantation and develop chronic vascular rejection more often and earlier than HCV negative recipients [16]. HCV is strongly associated with post transplant diabetes mellitus in renal transplant recipients and appears to account for the increased diabetogenicity observed with tacrolimus [8,63]. However, the clinical course of anti-HCV-positive recipients is less aggressive than that of HBsAg-positive recipients [2]. Patient and graft survival were not different in antiHCV-positive and antiHCV-negative kidney recipients irrespective of liver histology, and there was no difference in survival between antiHCV-positive and antiHCV-negative patients with chronic hepatitis [51]. HCV appears not to

cause aggressive liver disease in the early post transplant period [12]. It is concluded that HCV infection in patients under immunosuppressive therapy causes only a mild liver disease, as determined by clinicochemical and clinical parameters, and that mortality rate is not increased [26]. Moreover, previous results did not confirm a deleterious effect of the use of ATG (anti-thymocyte globulins) as induction therapy in these HCV-infected patients [55]. There were no differences in graft survival, overall mortality, or mortality secondary to liver disease or sepsis [40]. Based on these results, the presence of anti-HCV should not be a contraindication for kidney transplantation [19,34,35,37,47,58,60]. In addition, HCV-positive renal transplant recipients had a better survival than similar HCV-positive patients awaiting trans-plantation [36,49].

According to the results of the initial survey of the prevalence of HCV infection among the potential candidates for kidney transplantation, namely, the chronic hemodialysis patients in Egypt we initially faced a hard decision: to exclude these patients from the transplantation program. This decision was very difficult to consider, simply because it meant exclusion of more than 85% of the available willing candidates. So, the alternative was to run a prospective study looking for the outcome of kidney transplantation in such patients but after doing liver biopsy to every candidate who proves as HCV Antibody +ve. The study plan was initially based on exclusion of any of such HCV Antibody +ve candidates from the kidney transplantation program if his liver biopsy shows severe active hepatitis or active liver cirrhosis. The 1st 10 HCV+ve cases recruited in this study did not show either of such pathology pictures to exclude from the kidney transplantation program. In view of this finding, we decided not to perform further liver biopsy except in case that the liver transaminases are persistently and significantly high during the period of preparation or the abdominal ultrasonography shows signs of cirrhotic changes. This decision was based on benefit: risk ratio in such group of patients [22]. This decision is also supported by the conclusion that Liver biopsy is not indicated in deciding disease severity in patients with normal course of serum transaminases unless clinical findings dictate otherwise [6].

None of the eleven HCV Antibody +ve candidates recruited after taking this decision had shown any indication to perform liver biopsy according to the designed indications put by the group to do this procedure.

When polymerase chain reaction was later available to detect HCV ribonucleic acid of the virus genome, we tested all the surviving cases and the test was +ve in all HCV +ve cases, confirming their affection by this virus.

The immunosuppression protocol was kept identical in all cases of either group in order to avoid any change in the outcome that could be related to variations in such immunosuppression regimen. However, the evident elevation in serum bilirubin and/or hepatic enzymes obliged us to discontinue azathioprine in five cases (four cases in HCV +ve group and one case in the HCV -ve group). Follow up of liver and kidney functions in these five cases proved effectiveness and safety of this discontinuation except in 2 cases (one in each group) that showed slow consistent rise of serum creatinine. In these 2 cases mycophenolate mofetil (MMF) was successfully used instead of azathioprine as rescue therapy.

The patient and graft survival in the HCV +ve group was not statistically different all through the five years of follow up from those observed in the HCV -ve group. These results indicate that the presence of anti-HCV should not be a contraindication for kidney transplantation especially in Egypt where the prevalence of this virus infection among hemodialysis cases is overwhelming. Mortality was intimately related to liver cell failure in one case of either group obviating HCV as the offender in the etiology of this mortality.

On the other hand, in two of the remaining mortalities encountered in the HCV +ve group, malignancy was intimately related. In the 1st case multiple myeloma was discovered by the 32nd post-operative month, while the 2nd case had a high-grade non-Hodgkin lymphoma during the 43rd post-operative month. Genome similarities between HCV and flavivirus or pestivirus were reported and for this reason HCV has been included within the family Flaviviridae as a separate genus. Among the analogies between HCV and the other members of the same family, there is the possibility of infecting blood cells. In particular, significant evidence obtained through studies performed in vivo and in vitro support the concept that HCV is not only a hepatotropic but also a lymphotropic virus. This suggests that, in addition to playing a role in inducing hepatic diseases (both of a non-tumoral and a neoplastic nature), HCV infection may also play a role in extrahepatic pathologies. The striking association observed between HCV infection and some autoimmune-lymphoproliferative disorders of either benign or neoplastic nature is consistent with this hypothesis [67]. The most frequent biological peculiarity is Cryoglobulinemia, found in more than 50% of patients. It is only symptomatic in less than one-third of cases (as purpura, Raynaud's syndrome, neuropathy or renal failure), and could be the origin of benign lymphoproliferative hematological pathology, then of a malignant one, the non-Hodgkin lymphoma [17]. HCV-specific genomes have been reported in the sera of over 37% of patients with non-Hodgkin lymphoma of B-lymphocytes, not associated with Cryoglobulinemia [39]. Moreover, the 4-year probability of post-transplantation lymphoproliferative disorder (PTLD) was significantly higher in patients receiving a liver transplant for HCV-related cirrhosis than non-HCV liver diseases (12.3% vs. 2.2%, respectively; P=.015) [32]. The frequent involvement of extranodal sites characterizes the non-Hodgkin lymphoma complicating HCV infection [30]. In addition to non-Hodgkin lymphoma, chronic HCV infection has a substantial role in the etiology of other B-cell neoplasia including multiple myeloma [53].

Although continuously or intermittently elevated transaminases do not always indicate morphologically

advanced disease, the normal course of serum transaminases is mostly accompanied by normal, or near-normal, liver histology, in HCV-infected renal transplant patients [6]. This may also explain the near normal hepatic albumin and prothrombin synthesis in the HCV +ve group all through the 5 years of follow-up.

According to the available results, it seems that kidney transplantation in HCV infected chronic renal failure patients is safe if their serum transaminases is repeatedly near normal, the clinical and abdominal ultrasonography do not show marked hepatic dysfunction and/or the hepatic histopathology does not disclose severe hepatic affection.

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